CHAPTER XXI

SALMONELLA INFECTIONS

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INTRODUCTION

Near the turn of the century it was discovered that certain febrile diseases which bore a striking clinical resemblance to typhoid fever were caused not by the typhoid bacillus but by microorganisms which were culturally related to the so-called bacillus of hog cholera or swine plague first described by Salmon and Smith in 1886[33]. These microorganisms subsequently became known as paratyphoid bacilli and the febrile illnesses they produced in humans as the paratyphoid fevers. About the same time outbreaks of food poisoning of an infectional nature were found to be caused also by bacteria with the same morphological and cultural characteristics of the paratyphoid bacilli such as *Bacillus enteritidis* and *Bacillus aertrycke*. Many additional relatives of these bacteria now classified generically as *Salmonella* have been identified since then and as a group they have become recognized among the more important agents of infectious disease in the human subject.

Until 1925 the relationships among the various salmonella and the clinical patterns of the diseases they produce were with certain exceptions obscured by the fact that no reliable means existed for identifying precisely the individual bacterial species cultural methods for the differentiation of species have always been inadequate and their classification by serological techniques was, at that time incomplete and in a confused state During the last twenty years however, extensive immunological studies of the salmonella group initiated by White[41] and elaborated by Kauffmann [1] and others have provided methods for the accurate identification and classification of these microorganisms, while bacteriological procedures for their isolation especially from the feces have been greatly improved Our present knowledge of the epidemiology and clinical features of infections caused by salmonella is based largely on information gained through these contributions of the laboratory

Bacteriology

The genus *Salmonella* comprises a group of gram negative non sporulating bacilli that grow well on ordinary artificial culture media are motile by means of peritrichate flagellae ferment dextrose mannitol maltose and sorbitol with the formation of acid and gas fail to attack lactose sucrose and salicin and do not form indole or liquefy gelatin[4] Not all cultures however conform to these criteria and irregularities of behavior occur with sufficient frequency that it is difficult to frame a precise definition of the genus

The microorganisms are classified in the Kauffmann White schema [1] according to immunological differences among the somatic (O) and flagellar (H) antigens possessed by the various members of the group The somatic (O) antigens have been shown chemically to be complexes each consisting of a specific polysaccharide in combination with a phospholipid and a protein They are relatively heat stable, resist treatment with alcohol exhibit toxic properties when injected into animals or man and constitute the essential immunizing fraction of the bacteria[20] Individual species of salmonella usually contain two or three somatic antigens and at least thirty such antigens have been identified for the genus as a whole In the Kauffmann White classification the somatic antigens are designated by Roman numerals

The flagellar antigens apparently are proteic in nature although relatively little is known about their chemical structure They are heat labile, destroyed by alcohol and may be removed from the surface of the bacteria by repeated washing They apparently play little if any role in antibacterial immunity Individual salmonella usually possess several flagellar antigens which commonly exist in either one or both of two phases specific (phase 1) and non specific (phase 2) Those species, which exist in either the specific or non specific phase

alone are called monophasic while those which show fluctuation or variation between the specific and non specific phases are known as diphasic Diphasic variation between specific antigens is also known to occur in some species In the Kauffmann White classification the specific flagellar antigens of which more than 60 have been identified for the entire genus are designated by small Roman letters those discovered after the alphabet was exhausted being indicated by the letter z with a numerical subscript The non specific flagellar antigens are fewer in number 7 having been identified thus far and these are designated by arabic numerals

By this means of serological classification more than 150 distinct species of salmonella have been described to date and new ones are being reported constantly[4] Many of these species however have been isolated from animals or from birds alone and have not yet been associated with disease in man actually in practice there are less than 20 salmonella types which are found frequently in human infections These more important types and their antigenic formulae are listed in the accompanying table (Table I) It will be noted that the bacteria are divided into 5 groups A to E depending upon the possession of common somatic antigens there is a sixth group F which is not included since its members although numerous are encountered rarely

The names of individual salmonella species have been derived largely from those of the localities in which they were isolated originally and it is now an accepted procedure in nomenclature for new species to be designated in this manner using the names of town or communities or in the U S A of states This does not imply of course that the various strains are restricted to the areas of original isolation for example *S montevideo* first isolated in Uruguay has been found to be widely distributed throughout the United States and other parts of the world

The accurate identification of salmonella species by serological methods has proven to be of immense practical importance particularly from the epidemiological standpoint and it is the only means whereby a better understanding of the role played by these bacteria in various forms of human disease can be obtained The serological identification of all known species is possible only in certain salmonella centers where a large number of properly prepared antisera are available and is not within the province of the ordinary diagnostic laboratory A few specific O antisera however will suffice to detect the majority of salmonella and will readily enable group differentiation without of course distinguishing types Moreover since the salmonella most important in human infections are relatively few in number complete identification of more than 90 per cent of the common strains can be made using the technique suggested by Bornstein[3] which requires only 18 sera 6 O 11 monophasic H and a Vi serum This technique should be adopted generally by hospital and public health laboratories[5]

Salmonella antigens both somatic and flagellar have been found not infrequently in strains of *E coli* and other coliform bacteria (para colon bacilli) as well as in *Shigella*[4] The biochemical reactions of these organisms serve however, to distinguish them from salmonella

TABLE I

ABBREVIATED KAUFFMANN WHITE CLASSIFICATION OF THE COMMONER SALMONELLA

Types	Somatic Antigens	Flagellar Antigens	
		Phase 1	Phase 2
Group A			
S paratyphi A	(I) II XII	a	–
Group B			
S paratyphi B	(I) IV (V) XII	b	1 2
S typhi murium	(I) IV (V) XII	i	1 2 3
S derby	(I) IV XII	f g	–
Group C₁			
S cholerae suis (Kunzendorf type)	VI VII	–	1 5
S montevideo	VI VII	g m s	–
S oranienburg	VI VII	m t	–
S bareilly	VI VII	y	–
Group C₂			
S newport	VI VIII	e h	1 2 3
Group D			
S typhi (E typhosa)	IX (Vi) XII	d	–
S enteritidis	(I) IX XII	g m	–
S panama	I IX XII	l v	1 5
Group E			
S give	III X XXVI	l v	1 7
S anatum	III X XXVI	e h	1 6
S senftenberg	I III XIX	g t	–

Eberthella typhosa may be classified serologically with the salmonella although it is not strictly a member of this genus

Note Consult the text for an explanation of the symbols used to designate somatic and flagellar antigen

EPIDEMIOLOGY

Salmonella infections with the exception of the paratyphoid fevers ordinarily are not reportable and for this reason no accurate estimation can be made of the

total number or distribution of cases occurring annually in the United States However the over all incidence must be very large judged by the frequency with which outbreaks of food poisoning caused by these bacteria are reported[10] by the common occurrence of single or sporadic cases of infection and by the numerous strains identified each year from all sections of the country by salmonella centers such as those at the Kentucky Agricultural Experiment Station and the Beth Israel Hospital New York City

Sources of Infection

The microorganisms almost invariably invade the body by way of the gastro-intestinal tract usually following the ingestion of contaminated foodstuffs Milk and milk products are common sources of infection and the rôle of cream as a vehicle has been especially emphasized by Savage[24] bakery goods such as pies cakes cream puffs and puddings also are common modes of transmission Numerous outbreaks have been attributed to infected ducks eggs in Europe[4] where they are widely used and one such outbreak has been reported in the United States[8] Meats and meat products particularly pork have been found frequently to be contaminated with salmonella[7] and are known to be a common source of human infection Outbreaks involving frozen fish and smoked fish have been described also[3]

It may be noted that salmonella infections unlike typhoid fever are rarely water borne As indicated above the usual sources of infection are articles of food in which the bacteria may not only survive but also multiply and it has been shown for example that salmonella multiply rapidly in fresh raw milk and survive at least two months in various grades of salted and unsalted butter[31] The conclusion to be drawn is that in most instances these microorganisms have a relatively low pathogenicity for the human and that considerable numbers must be ingested before clinical manifestations of infection become evident

Foodstuffs may be contaminated with salmonella either directly or indirectly In the case of meats and eggs the bacteria may be derived directly from animals or poultry as a result of the carrier state Chickens ducks and turkeys are frequent carriers and salmonella have been isolated from the mesenteric lymph nodes of apparently healthy swine both in this country and in South America[7] Cows also may be asymptomatic carriers and transmit the infection through their milk[3?]

Animals and human carriers usually are responsible for the indirect contamination of foods A significant proportion of healthy rats trapped at random may be found to have salmonella in their feces[2?] and cases of human infection have been traced to food soiled with the excreta of these rodents Salmonella have been isolated also from horses dogs and cats, although only in the case of the dog

has transmission to man been known to occur The role of the human carrier is of great interest but not entirely clear at the present time Salmonella infections in the human with the possible exception of those caused by *S paratyphi A* and *S paratyphi B* rarely result in a prolonged carrier state as is so often the case in typhoid fever Nevertheless the microorganisms often continue to be excreted in the feces for weeks or months after clinical signs of an infection have subsided Of equal or greater importance is the fact that healthy persons with no antecedent history of infection may be asymptomatic carriers[1] In many cases these individuals have been in contact with diseased persons or have eaten articles of infected food which provoked symptoms in others but caused only subclinical infection in themselves Surveys have shown that these asymptomatic carriers are much more numerous among the general population than was formerly thought and obviously if they are employed as food handlers dairy workers or in hospitals there are great opportunities for the transmission of their unsuspected infection Stone[31] detected 40 salmonella other than *S typhi* in repeated stool examinations among 2 000 food handlers in the Panama Canal Zone while Seligmann Saphra and Wassermann[26] found 89 healthy carriers among 1 000 cases of salmonella infection of these 5 were food handlers 1 was a dairy worker 2 were kitchen maids and 3 were student nurses The significance of these findings is readily apparent

Insects may also be vectors of salmonella Ostrolenk and Welch[29] showed that houseflies infected with *S enteritidis* are capable of infecting other flies as well as food water and surfaces with which they come in contact Transfers of the infection from flies to mice and vice versa were successful, and fly eggs in mash containing *S enteritidis* gave rise to infected larvae pupae and adults

Sex and Age Distribution

The meager data available indicate that salmonella infections have a rather uniform sex distribution males and females being about equally affected Such information has been secured mainly from a study of sporadic cases since in outbreaks involving multiple cases from a single source as in hospitals asylums, military establishments social gatherings and the like the data may be heavily weighted in favor of one sex or the other The lack of sex predilection is similar to that observed for most infectious diseases

No age group is immune In the series of 1 000 cases reported by Seligmann Saphra and Wassermann[26] the youngest patient was 2 days old and the oldest 78 years of age However there is general agreement that most cases occur among infants children and young adults A remarkable number of infections are seen in babies less than one year of age and salmonella are recognized as one of the important etiological agents in the summer diarrhea of infants[19] Approxi

mately 40 per cent of all salmonella infections occur in children under the age of 10 years

Seasonal Incidence

Salmonella infections occur throughout the year but as with typhoid fever and bacillary dysentery their greatest incidence is in the warm months In the United States cases begin to increase in numbers about April and become increasingly prevalent until a peak is reached in October thereafter they decline rapidly although a slight rise may be observed during the Christmas season In Montevideo Uruguay Hormaeche and Peluffo found that 83 per cent of the cases occurred between November and April which are the summer months in South America[19]

Distribution of Salmonella Types

The extensive studies on the occurrence and distribution of salmonella types in the United States by Edwards and Bruner[9] and by Seligmann and associates[15] indicate that the common types are in a sense ubiquitous while even the rarer members with few exceptions are not confined to any given areas For a more detailed discussion the types may be considered according to their serological grouping in the Kauffmann White classification (Table I)

In group A *S paratyphi A* is the only important member For some unexplained reason this type is now seen much less frequently in the United States than it was some 20 years ago For example among 532 strains of salmonella isolated from human infections Edwards and Bruner[9] found only 7 strains of *S paratyphi A* In other parts of the world however the type is encountered often particularly in the Orient

In group B *S typhi murium* often referred to as *S aertrycke* is the most widely distributed of all salmonella types and is the chief cause of salmonella gastroenteritis This organism apparently can produce disease in all species of warm blooded animals and is important in animal husbandry and poultry farming as well as in human medicine *S paratyphi B* also is encountered frequently and usually is observed in association with human infection however the organism has been isolated from healthy horses cows and swine which must be considered as potential reservoirs of enteric fever Other members of group B such as *S derby* *S chester* *S sandiego* and *S bredeney* may produce disease in man but are predominantly found in animals and poultry

A number of important salmonella types are found in group C First among these is *S cholerae suis* the type species of the genus long recognized as an animal pathogen particularly in swine but also responsible for severe infections in man Most strain of *S cholerae suis* isolated in the United States are of the monophasic

Kunzendorf or so called European type *S oranienburg*, *S montevideo* *S bareilly* and *S newport* which are primarily animal strains frequently infect man and usually cause an acute gastroenteritis Types seen less commonly include *S thompson* *S muenchen* *S oregon* *S manhattan* and others *S paratyphi C* (Hirschfeld) is very rarely found in this country

The important members of group D excluding *S typhi* are *S enteritidis* and *S panama* *S enteritidis* is found primarily in rodents, and human infections with this type probably arise in the main from that reservoir *S panama* on the other hand is found much more frequently in man than in lower animals and should be considered essentially a human pathogen Occasionally other strains make their appearance such as *S dublin* *S sendai* and *S eastbourne*

Types of group E are found fairly frequently in both man and animals *S anatum* *S give* and *S senftenberg* are the commonest members Among others less common are *S meleagridis* *S lexington* and *S newington*

Group F embraces a large number of strains which for the most part have been revealed thus far to have only local distribution They have been isolated from animals poultry and humans and are of considerable interest epidemiologically although of lesser importance from the clinical standpoint Two types in this group *S havana* and *S wichita* identified with outbreaks of human infection in the communities of origin have not been discovered subsequently

Clinical Aspects

It was formerly customary to divide salmonella infections into two main clinical groups 1) so-called paratyphoid fever caused by essentially human pathogens such as the paratyphoid A and B bacilli and 2) acute gastroenteritis or food poisoning caused by strains primarily pathogenic for animals such as *S typhi murium* and *S enteritidis* This classification was based on the now outmoded Kieler Lehre or doctrine of Kiel[18] which postulated that the human pathogens always provoked a clinical syndrome characterized by continued fever of the typhoidal type while the animal species when transmitted to man caused only localized infections of the gastrointestinal tract with nausea, vomiting and diarrhea More recently however with our widening knowledge of salmonella infections acquired chiefly through the more precise serological recognition of strain differences a new concept has been developed In essence the concept is that any species of salmonella capable of infecting man may produce any of the following clinical syndromes or states

1) continued fever of the typhoidal or enteric type
2) acute gastroenteritis
3) localized infections with or without an accompanying sepsis
4) asymptomatic infections or carrier states

Clinical experience has shown it is true that certain types of salmonella do cause continued fevers and septic infections more frequently than they cause gastroenteritis and vice versa but these facts do not invalidate the concept which may be illustrated in part by findings such as those of Warren[40] in a group of 56 persons infected with *S paratyphi B* Seven of these individuals developed typical typhoidal or enteric fever after an incubation period of 6 to 1 days 17 others developed diarrhea from 12 to 72 hours after infection passing imperceptibly into enteric fever another 17 cases had early gastrointestinal symptoms of nausea vomiting abdominal pain and diarrhea then a remission followed by enteric fever 9 cases had only early acute gastrointestinal symptoms and 6 cases remained asymptomatic but yielded positive stool cultures Finally 2 persons continued to carry the organism 10 months after infection

Continued or Typhoidal Fever

The continued or typhoidal type of fever often referred to as paratyphoid fever is a common clinical manifestation of salmonella infection The strains most frequently responsible for this clinical syndrome are *S paratyphi A S paratyphi B S cholerae suis* and *S panama* As in typhoid fever the incubation period is prolonged ranging from 5 to 6 days up to 2 weeks

The onset of symptoms usually is insidious the temperature showing a step-like rise with increasing malaise headache lassitude and anorexia often with chills and occasionally with nausea and vomiting or the onset may be abrupt with a rapid rise in temperature accompanied by chills and sweats Shaking chills are seen more frequently in the salmonella fever than in typhoid fever In uncomplicated cases the fever ordinarily lasts for a few days up to 2 week but febrile relapses are common so that the illness may be prolonged for several weeks or even longer The fever is sustained in about 25 per cent of cases in the remainder rather wide daily fluctuations in the temperature are observed In general the disease is milder than typhoid but it may be severe and a fatal outcome is not infrequent particularly in infants and in aged or debilitated persons

Other clinical features parallel to a large extent those seen in typhoid fever[1] Headache is almost always present and other cerebral manifestations may occur including dizziness apathy stupor coma and delirium Muscular aches and pains particularly pain in the back are common Herpes labialis is observed occasionally Epistaxis is not infrequent Cutaneous lesions occur in many cases usually consisting of rose spots on the chest back or abdomen which appear during the second week of the illness papular petechial and purpuric eruptions have been described but are rare Tracheobronchitis is common with a hacking non productive cough and in severe cases bronchopneumonia may develop Diarrhea may accompany the onset of the disease but during the phase of con

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5 to 10 loose stools daily over a period of 1 to 5 days together with a low grade fever

During the acute phase of the illness there is usually abdominal tenderness often localized to one or both of the lower quadrants and the abdominal signs may resemble those seen in acute appendicitis[4] The infection almost always is confined to the intestinal canal although in some cases the responsible agent may temporarily invade the blood stream

Salmonella gastroenteritis is a benign infection on the whole but the mortality rate in infants is relatively high especially during the first year of life

Localized Infections

Salmonella may cause localized infections anywhere in the body either with or without an accompanying sepsis Localized infections with all of the commoner species of salmonella have been reported but the strain most frequently responsible is *S cholerae suis* which has pronounced invasive characteristics

Cholecystitis and Cholangitis — Acute cholecystitis and cholangitis are common complications of systemic infections with salmonella they may appear also independently as localized infections The clinical manifestations include fever leucocytosis localizing signs in the right upper quadrant and often jaundice Salmonella may be responsible also for chronic cholecystitis either with or without biliary calculi and operative intervention in such cases may be followed by acute exacerbations of the infection often characterized by an acute gastroenteritis The peculiar relationship of surgical procedures to the exacerbation of chronic or latent salmonella infections has been emphasized by Harvey[1]

Endocarditis — Both acute and subacute bacterial endocarditis have been reported[11] The clinical features of the disease do not differ significantly from those of endocarditis caused by other bacteria and the diagnosis can be made only by identification of the causative agent in the laboratory usually from cultures of the blood

Meningitis — Infection of the meninges is by no means uncommon[9] It occurs most frequently in infants and children and is seen rarely in adults The meningitis may be either primary or secondary to infection elsewhere in the body usually in the gastrointestinal tract and almost invariably is fatal

Pneumonia and Empyema — The lungs often are the site of predilection for localized salmonella infections[1] Both lobar pneumonia and bronchopneumonia have been described and the bacteria have been isolated from the sputum The pneumonia may be accompanied or followed by a pleural effusion or empyema

Osteomyelitis and Pyarthrosis — The bones and joints are frequent sites of localization[30] Infections of the bone marrow usually occur near the joints and the symptoms are those seen with any acute pyogenic osteomyelitis together with

tinued temperature elevation the majority of patients exhibit constipation and tympanites A smaller group have alternating constipation and diarrhea Intestinal hemorrhage and perforation are much less common than in typhoid Jaundice may be seen in association with a complicating acute cholecystitis or cholangitis Cardiac and renal failure may occur but are due usually to pre existing conditions accentuated by the superimposed infection Acute glomerulonephritis has been reported but is rare

Among the physical findings a relative bradycardia may be noted during the febrile period as in typhoid but occurs less often than in the latter disease Pulmonary involvement may be indicated by the presence of fine crepitant rales in the absence of more definitive signs of bronchopneumonia The spleen becomes palpably enlarged in the majority of cases less commonly the liver is enlarged as well Abdominal tenderness frequently develops and a generalized lymphadenopathy is observed sometimes

There are no characteristic changes in the blood count Some cases show a leucopenia with a relative lymphocytosis while others have normal counts or a leucocytosis with an absolute increase in polymorphonuclear neutrophiles There is no correlation between the character of the leucocytic response and the type of the infecting organism although leucopenia apparently is seen less frequently with infections caused by *S cholerae suis* than with *S paratyphi* A and *B* In many cases a moderate anemia develops during the course of the disease The urine usually contains variable amounts of albumin together with leucocytes and granular casts as in other febrile diseases

The bacteriological and serological findings are discussed in the section on Diagnosis

Gastroenteritis

Acute gastroenteritis is the commonest clinical syndrome caused by infection with the salmonella and often is referred to as one of the types of food poisoning The causative agent most frequently is *S typhi murium* while other strains often encountered include *S newport S montevideo S oranienburg* and *S enteritidis* The incubation period is short occasionally being only a few hours and in most cases is from 1 to 36 hours

The usual symptoms are those of nausea vomiting abdominal cramps profuse watery diarrhea and fever and the disease may readily be confused on clinical grounds alone with bacillary dysentery although the stools rarely contain blood [7] Cases vary considerably in their severity from those having only a brief diarrhea with no constitutional reaction to others that present a clinical picture closely simulating cholera with prolonged exhausting diarrhea marked dehydration and shock Ordinarily however, the disease is moderate in intensity with

isms and although the diagnosis may be entertained in patients showing a typhoid like illness or an acute gastroenteritis the final proof always rests on the results of bacteriological examinations for the causative agent in blood feces urine and other body fluids or in purulent exudates and on serological tests for the development of specific antibodies in the blood of the host

In typhoidal infections salmonella usually invade the blood stream early in the course of the disease just as the typhoid bacillus does in typhoid fever and a prompt diagnosis is therefore most readily made by blood culture The organisms also regularly appear in the blood in cases of endocarditis and in sepsis which may be associated with any of the other localized infections including those of the gastrointestinal tract Cultures of the blood are best made by seeding 5 c c portions of blood drawn with aseptic precautions into flasks containing about 100 c c of beef infusion broth it is also frequently helpful to make pour plate cultures by accurately pipetting 1 or 2 c c of blood into 10 c c of melted and cooled nutrient agar in petri dishes Growth takes place rapidly at 37 C and is revealed in the liquid cultures by diffuse clouding of the media in 24 to 48 hours with motile gram negative bacilli The confirmatory biochemical and serological tests on the organisms then are performed In the pour plate cultures single bacilli give rise to colonies which can be counted macroscopically or with the aid of a hand lens thus enabling one to count the number of bacteria per c c of blood and to estimate the degree of bacteremia

Salmonella usually appear in the feces of patients with typhoidal infections during the second week of the illness and may continue to be excreted for variable periods of time during convalescence or even longer if the carrier state develops Cultures of the feces are valuable in diagnosis and for follow up studies on such patients* In salmonella gastroenteritis fecal culture is the only reliable method whereby a diagnosis may be made For best results fecal cultures should be made according to the technique of Kauffmann[1] in which the specimens are first inoculated into tetrathionate brilliant green broth incubated for 18 hours and then subcultured on non selective plated media such as eosin methylene blue agar or MacConkey s agar and on selective media such as SS agar (Difco) or desoxycholate citrate agar[17] The preliminary cultivation of the feces in tetrathionate broth permits uninhibited growth of salmonella but restricts the growth of the coliform bacteria which are normally present thus increasing the opportunity to isolate the pathogenic organisms from the plate cultures In many laboratories however cultures are made directly on the plated media without preliminary enrichment in tetrathionate broth with good results especially if SS agar is employed In either case colonies of non lactose fermenting organisms are transferred from the plates to differential media and strains showing the biochemical reactions of salmonella then are subjected to serological analysis

Salmonella in the urine in body fluids and in purulent exudates are isolated

the characteristic x ray changes as the disease progresses Salmonella apparently may reside for long periods of time in the bone marrow without provoking symptoms

Pyarthrosis is characterized by swelling warmth and tenderness of the involved joints Aspiration yields purulent exudate from which the organism ordinarily can be recovered by cultural methods

Infections of the Urinary Tract — As previously mentioned, salmonella may excite an acute nephritis in association with systemic infections of the typhoidal type More frequently however the infections of the urinary tract are localized and are unaccompanied by signs of infection elsewhere in the body[13, 30] Cystitis pyelitis pyelonephritis and perinephric abscess have all been described It is worthy of note that pyelonephritis caused by salmonella has been reported in a number of patients with renal calculi

Other Localized Infections — In children salmonella not infrequently cause an acute pharyngitis or tonsillitis sometimes associated with suppurative otitis media[16] These localized infections of the upper respiratory tract and the middle ear are uncommon in adults

Acute appendicitis is observed occasionally although in most cases of gastroenteritis with signs confined to the right lower quadrant the appendix is found to be innocent and the signs and symptoms may be attributed to an acute cecitis

Several cases of salpingitis have been reported[36] Other localized infections that have been described include pericarditis subdural abscess splenic abscess breast abscess subcutaneous abscesses infected myoma of uterus pelvic abscess ischiorectal abscess and abscess of the sacrolumbar region[8, 25, 30]

Asymptomatic Infections or Carrier States

Apparently healthy persons may excrete salmonella in their feces for variable periods of time either as the result of asymptomatic infections or following clinically manifest disease such as typhoidal fever or gastroenteritis The foci of infection from which the bacilli continue to be excreted are in many instances not detectable but it is probable that in most cases the focus is the gall bladder or the biliary passages Hewer[14] has reported an interesting case of fatal infection with *S paratyphi B* in which enormous numbers of bacilli were found in the bile canaliculi without any surrounding tissue reaction suggesting that in the carrier state the organisms may proliferate in this site without harm to the host

Diagnosis

The diagnosis of an infection with salmonella is difficult to make on clinical grounds alone because of the varied patterns of disease produced by these organ

the enormous reservoir of salmonella pathogenic for man among domesticated animals and poultry as well as in rodents such as rats and mice whose habits of life bring them into intimate contact with human beings From this reservoir new infections are being communicated constantly from animals and birds to man usually through the medium of contaminated foodstuffs and at the present time there are no practicable means for preventing this transmission except through the careful inspection and bacteriological examination of food products These procedures however leave much to be desired

The problem of the identification and control of human carriers of salmonella is much more difficult than for typhoid carriers The typhoid carrier is almost invariably a person who has suffered from the disease and continues to excrete bacilli more or less constantly for long periods of time thereafter The salmonella carrier on the other hand frequently has had no clinical manifestations of his infection and may excrete the organisms in the feces and therefore be a potential vector for only a few days or weeks he usually remains undetected unless discovered by chance or by routine survey Perhaps the best method for reducing the incidence of salmonella infections transmitted by human carriers is the control through frequent fecal culture of all food handlers kitchen employees nurses and other personnel who work in restaurants packing houses institutions hospitals and the like

Vaccine prophylaxis of salmonella infections has been found to be effective against *S paratyphi A* and *B* and these strains are included in the so-called triple typhoid or TAB vaccine which is used by the United States army and navy[4] and in most civilian programs for immunization against typhoid fever but the full possibilities of prophylactic vaccination against salmonella have by no means been fully realized An important step forward should be the inclusion in the vaccine of an appropriate C group strain since infections with salmonella of this group are widespread and of great clinical importance such a step has been taken already in Great Britain where a TABC vaccine is now being used It should be noted in this connection however that additional evidence is needed to determine whether vaccination with single strains of salmonella from the various groups as defined by the Kauffmann White classification will confer protection against other members of the same serological groups Furthermore although there is reasonable proof that the present TAB vaccines will largely prevent typhoidal infections with *S paratyphi A* and *B* which have a long incubation period the usefulness of these and newer vaccines of wider valency in preventing acute gastroenteritis where the infection has a short incubation period and is essentially of a body surface is a question that must remain sub judice for the moment

Recent studies have shown that the essential immunizing fractions of the typhoid bacillus and of *S paratyphi A* and *B* can be extracted from the bacilli

most readily by culturing the materials on the plated media previously mentioned

Examination of the patient's blood for the detection of specific antibodies (Widal test) is a helpful diagnostic procedure and should be carried out always in any case of suspected salmonella infection. It is wise to perform a series of tests on samples of blood drawn early in the disease and at intervals thereafter in order to evaluate changes in antibody titer as they occur, significant titers of antibody usually developing within two weeks after the onset of the disease. The antibody response in general is less pronounced and more variable in purely gastrointestinal infections than in systemic infections where the organism has entered the blood stream, and it is related also in some measure to the severity of the disease.

The classical type of Widal test as done in many laboratories for typhoid and for paratyphoid A and B frequently will give an entirely deceptive result in cases of salmonella infection. Such tests fail to detect antibodies to salmonella of the C group, which are of major clinical importance, and the results vary within wide limits depending on whether alcoholized, formolized or living antigens are employed. To obtain a precise serological picture, a Widal test with sharply specific antigens should be performed as in the following procedure recommended by Seligmann, Saphra and Wassermann[35] which uses seven antigens

		Somatic Antigen	Flagellar Antigens
1	Alcoholized *S. derby*	IV	
2	Alcoholized *S. oranienburg*	VI, VII	
3	Alcoholized *S. enteritidis*	IX	
4	Formolized *S. urbana*	(XXX)	b–
5	Formolized *S. kentucky*	(VIII, XX)	i–
6	Formolized *S. muenchen*	(VI, VIII)	d–
7	Formolized *S. newport*	(VI, VIII)	– 1 3

No antigen of *S. paratyphi* A is included because the type is encountered rarely.

By the use of such a Widal test not only will a specific antibody response to salmonella infection, including *S. typhi*, be detected readily, but even the exact nature of the infecting strain may be predicted in many cases. It should be noted, of course, that the evaluation of the serological pattern must take into account whether or not the patient has received previously injections of typhoid-paratyphoid vaccine.

Prevention and Prophylaxis

The public health measures responsible for the control of typhoid fever, which is primarily a water-borne disease of humans alone, have been largely ineffective in the prevention of salmonella infections. Probably the chief reason for this is

In localized infections surgical procedures are employed where indicated

In caring for patients with salmonella infections it is advisable to adopt the isolation precautions which appear necessary to prevent communication of the infection to other persons

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by chemical means and that exceedingly small amounts of these substances which are protein polysaccharide in nature will engender specific antibody responses in man and in experimental animals greater than those produced by standard doses of whole bacterial vaccine and without unpleasant local or systemic reactions[6] There is no question that vaccines of known chemical composition and potency prepared in this manner will replace eventually the present vaccines which are crude suspensions of killed bacteria varying in potency and containing much material which is not only toxic but also immunogenically inert

Treatment

There is no specific therapy for infections caused by salmonella although it is possible that new antibiotic agents such as streptomycin may be found to be effective The experience with streptomycin in the treatment of typhoid fever thus far has been disappointing

The sulfonamides particularly the more active compounds such as sulfadiazine and sulfathiazole exercise some bacteriostatic action on various strains of salmonella in vitro[39], but they have been found to have little if any, value in the treatment of human infections although in cases of gastroenteritis or in carriers they may reduce the number of organisms excreted in the feces without however eliminating them completely

Penicillin in very high concentrations is effective in vitro against salmonella but in clinical practice it has no effect

In cases of salmonella gastroenteritis with much diarrhea and fluid loss appropriate supportive treatment is essential and at times may be life saving Replacement of fluids and electrolytes by the parenteral administration of physiological solution of sodium chloride sometimes is necessary on a large scale guided by the general appearance of the patient the temperature pulse and arterial pressure the flow of urine and its specific gravity and whenever possible by determinations of the plasma carbon dioxide chloride and non protein nitrogen In severe cases with shock transfusions of whole blood or plasma should be used as needed

In medication for the relief of symptoms the salicylates should be employed with caution since many patients particularly those with salmonella infections of the typhoidal type react badly to their administration as do cases of typhoid fever Camphorated tincture of opium is very useful for controlling the abdominal cramps and to a certain extent the diarrhea in patients with acute gastroenteritis Neostigmine sulfate by injection may be used to relieve tympanites if given carefully

In the typhoidal fevers and in gastroenteritis the diet should be bland high in protein low in fat and moderate in carbohydrate content Fluids should be forced to maintain a urine volume of at least one liter per day

In localized infections surgical procedures are employed where indicated

In caring for patients with salmonella infections it is advisable to adopt the isolation precautions which appear necessary to prevent communication of the infection to other persons

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CHAPTER XXII

BACILLUS COLI INFECTIONS

By JOSEPH L MILLER

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Bacteriological Considerations

The colon bacillus is widely distributed in nature and has been isolated from air water and soil It is almost constantly present in the intestinal tract of man and some of the higher mammals It may be found in almost pure culture in the large intestine In the small bowel it is found in association with other bacteria It has been cultured from the feces of infants within four hours after birth When present in soil or water its presence may be attributed to contamination from the feces of man It is commonly present on the genitalia of women and is frequently found in vaginal discharges This probably accounts for its presence in puerperal infections The colon bacillus is quite resistant to heat Ayers and Johnson have shown that in milk when pasteurized as ordinarily carried out *i e* heated to 60 C (140 F) for twenty to thirty minutes only 54 per cent of colon bacillus culture was killed at 62 8 C (145 F) only 6 9 per cent survived and a temperature at 65 6° (150°F) killed all cultures

Ordinarily as it exists in man in the intestinal tract it is a harmless parasite When it invades other structures either alone or in conjunction with other bacteria it may give rise to serious pathologic changes Its pathogenicity in man has probably been overestimated Failure to differentiate between bacillus enteritidis and bacillus coli is responsible for some of these errors The common occurrence of agonal or post mortem invasion of the body by the colon bacillus diminishes the value of many reports regarding

its pathologic significance No doubt in many inflammatory processes in or adjacent to the intestinal tract the lesions are due to associated pyogenic bacteria rather than the bacillus coli

There is no doubt however that under certain conditions the colon bacillus may involve various organs and give rise to definite changes No one denies its etiological relation to inflammatory processes in the gall bladder and urinary tract It has also been reported at times as an important factor in the infection of wounds When pure cultures are injected into the serous cavities of rabbits the animal may die with a septicemia or, if the culture is less virulent a fibrinous or suppurative inflammation may develop The conditions under which the colon bacillus passes through the intestinal tract into the blood or lymph channels are not clearly determined A lesion of the mucosa the result of trauma or inflammation is probably essential Slight trauma resulting from intestinal contents is probably very frequent

Although the colon bacillus is a continual inhabitant of the intestinal tract an immunity is not acquired by the individual at least as determined by the agglutination phenomenon When however the bacillus invades the organs of the body the reaction of agglutination may develop Reports upon the presence of an agglutination reaction in normal individuals are at variance Some have reported the reaction frequently present in dilution of 1 to 100 others have been unable to verify these results

Role in Anemia

Experimentally the colon bacillus can produce a marked anemia Charlton[1] was able to produce in rabbits by repeated intravenous injection of colon bacilli a high degree of anemia with poikilocytosis and nucleated red cells Furthermore the animals developed spinal cord symptoms resembling somewhat those observed in pernicious anemia in man At autopsy there was a degeneration of the posterior and lateral columns of the lumbar cord Ludke and Fejes[2] report the isolation of a hemolytic lipoid from the colon bacillus By injecting this substance into rabbits dogs or monkeys they claimed to have produced a condition similar to pernicious anemia in man The color index was high and numerous nucleated red cells including megaloblasts appeared in the blood

Cystitis and Pyelitis

The colon bacillus is the most frequent cause of infection in the urinary bladder and pelvis of the kidney Albaran Halle and Legrain[3] in 1898

collected 304 cases of cystitis from the literature and in 131 or 42 7 per cent the bacillus coli was present In 89 or 20 2 per cent it was found in pure culture Brown[4] in 26 cases of postoperative cystitis in women probably due to catheterization reported the colon bacillus in 57 7 per cent In 24 cases of chronic cystitis with or without pyelitis the colon bacillus was found in 45 per cent and in 12 cases of chronic pyelitis in 50 per cent Scheidemandel[5] in 100 infected urines reported bacillus coli present in 85 Lenhartz[6] found the colon bacillus responsible for the infection in 66 out of 80 cases of pyelitis Keyes[7] considers the colon bacillus responsible in 90 per cent of cases of pyelitis

In addition to inflammatory processes in the urinary tract the colon bacillus is a frequent cause of bacilluria Especially the urine of children may contain the bacilli without evidence of inflammation Ross[8] found the colon bacillus present in the urine in forty per cent of apparently healthy children

The manner in which the infection occurs is still a matter for discussion Animal experimentation has shown that the intravenous injection or introduction into the urinary tract of animals of bacillus coli does not give rise to infection Obstruction to the outflow of urine or traumatization is essential in order to develop an inflammatory process In man colon bacilli very frequently pass into the urine from the blood In case the drainage is good no evil results follow If however there is retention or the presence of a foreign body in the kidney or bladder an inflammatory process may result

The infection in the bladder may arise from instrumentation According to Brown[4] the colon bacillus is present in the urethra of twenty per cent of healthy women In pelvic operations on women catheterization plus traumatization of the bladder is the usual cause of the colon bacillus cystitis An ascending infection of the urethra due to the colon bacillus might reach the bladder but probably this rarely occurs Extension through the lymphatics from the vagina or rectum is also a possible but probably unusual method of infection The hematogenous origin of cystitis is of frequent occurrence Instrumentation and secondary infection from the kidney are the other channels through which infection occurs Occasionally colon bacillus infection of the urinary tract follows evidence of marked intestinal disturbance with either diarrhea or stubborn constipation Here massive infection of the kidney of hematogenous origin may be responsible for the trouble

Pyelitis is usually due to a hematogenous infection The other channel through which infection may occur is along the lymphatics in the mucosa and submucosa of the ureter When ascending infection from the bladder develops it is through this route and not by direct extension along the lumen

of the ureter. Direct infection of the right kidney may occur through the network of lymphatics connecting the hepatic flexure of the colon with the kidney. Franke[9] reports that there is a lymphatic connection between the cecum and ascending colon and the right kidney and this is a factor in the more frequent involvement on this side. The symptoms of pyelitis vary greatly. The infection may be present for months or even years without giving rise to any inconvenience. Many times the first evidence of trouble is a severe pain in the loin often radiating toward the bladder. With this there may be chill with high fever. These sudden attacks are usually due to interference with the drainage from the kidney. Intermittent attacks of fever of unknown origin should direct attention to the kidney. Microscopical examination of a freshly passed specimen of urine will readily detect any marked renal infection, always bearing in mind the possibility of ureteral obstruction interfering with the flow of urine from the involved kidney. Cultures are necessary to verify the character of the infectious agent. The involved kidney is often tender to palpation. As the normal kidney is not sensitive to moderate pressure the presence of tenderness should excite suspicion. When colon bacilli are present in the urine without signs or symptoms pointing to the kidney a cystoscopic examination with ureteral catheterization is necessary to determine the source of the infection. The reaction of the urine is probably always acid in pure colon bacillus infections as this microorganism has not the power to form ammonia from urea. Primary pyelitis is much less frequent in men than in women. Lenhartz[6] in eighty cases had only six in males. It is quite frequent in female infants.

Smith reports a case of epididymitis complicating typhoid where the colon bacillus was found in the urine and also in fluid obtained from the epididymis. Reynolds also reports a case complicating a colon bacillus infection of the urinary tract.

The prognosis in urinary infection depends somewhat on the predisposing factors responsible for the infection. In case free drainage of the kidney or bladder can be established and this can be maintained a cure even of chronic cases may be expected. When the outflow of the urine is interfered with permanent cures are difficult or impossible until the obstruction has been removed. Prophylactic measures are very limited. Care in catheterization is perhaps one of the most essential. The treatment of acute cystitis should include rest in bed and the taking of large amounts of fluids. As formalin is very apt to increase the vesical irritation it is usually inadvisable to administer hexamethylenamin. Alkaline diuretics as the citrate and acetate should be given in sufficient doses to neutralize the urine and thus lessen the distress. It is not considered advisable to irrigate or introduce germicides into the bladder during the very acute stage. When the acute condition has subsided hexamethylenamin 15 grains (1 gm.) should be given four or five

times daily depending on the patient s tolerance and at the same time acid sodium phosphate in doses of 15 to 30 grains (1 to 2 gms) three times daily in order to render the urine strongly acid After a few days this medication may be replaced by alkaline diuretics This frequent changing of the reaction of the urine is thought to have a beneficial effect

In the subacute and chronic types irrigation is still advocated by a few but is much less popular than formerly This irrigation may be carried out with a saturated solution of boric acid or silver nitrate solution 1–1 000 to 1–2 000 Some advise after irrigating the bladder the introduction of ½ oz (15 c c) of a one to three per cent solution of silver nitrate In place of the silver nitrate a ten per cent argyrol solution ½ to 1 oz (15 to 30 c c) may be used

In case the bladder contains a foreign body it is necessary to remove it before a cure can be hoped for Urethral stricture should be treated as free drainage of the bladder is one of the essentials for a cure

The treatment of pyelitis in case there is definite pyrexia can be t be instituted by a short period of rest in bed The diet depends somewhat upon the reaction of the urine desired in the particular method of treatment If it is desired to reduce the acidity of the urine fruits and green vegetables should be given freely If it is decided to maintain a high degree of acidity the fruits should be restricted As functional impairment of the kidney is quite frequently associated with a pyelitis as shown by the increased blood urea the protein should be restricted Abundant water drinking is desirable While this lessens the concentration of any bactericidal agent the flushing out of the kidney is of greater importance Hexamethylenamin in a 15 grain (1 gm) dose three or four times per day is of great value The larger the dose tolerated the better the result In some individuals even moderate doses cause vesical irritation If this does not develop an effort should be made to give 60 to 75 grains (4 to 5 gms) daily Not infrequently hematuria develops This probably originates in the bladder and is not an evidence of renal irritation It is desirable however in case hematuria develops to lessen the dosage of the drug As hexamethylenamin is only active in acid medium it is necessary to maintain a high degree of acidity of the urine This can best be accomplished by the use of acid sodium phosphate in doses of 15 to 30 grains (1 to 2 gms) three times per day Although the bacillus coli grows in acid urine a high degree of acidity is detrimental to its growth (Meyer Betz[10]) Some prefer to change the reaction of the urine at intervals giving alkalies freely for a few days followed by hexamethylenamin and acid sodium phosphate

Catheterization of the ureter and irrigation of the pelvis of the kidney has many supporters and in skilled hands is a desirable method of treatment Probably one factor in the improvement following this treatment is improved

of the ureter Direct infection of the right kidney may occur through the network of lymphatic connecting the hepatic flexure of the colon with the kidney Franke[9] reports that there is a lymphatic connection between the cecum and ascending colon and the right kidney and this is a factor in the more frequent involvement on this side The symptoms of pyelitis vary greatly The infection may be present for months or even years without giving rise to any inconvenience Many times the first evidence of trouble is a severe pain in the loin often radiating toward the bladder With this there may be chill with high fever These sudden attacks are usually due to interference with the drainage from the kidney Intermittent attacks of fever of unknown origin should direct attention to the kidney Microscopical examination of a freshly passed specimen of urine will readily detect any marked renal infection always bearing in mind the possibility of ureteral obstruction interfering with the flow of urine from the involved kidney Cultures are necessary to verify the character of the infectious agent The involved kidney is often tender to palpation As the normal kidney is not sensitive to moderate pressure the presence of tenderness should excite suspicion When colon bacilli are present in the urine without signs or symptoms pointing to the kidney a cystoscopic examination with ureteral catheterization is necessary to determine the source of the infection The reaction of the urine is probably always acid in pure colon bacillus infections as this microorganism has not the power to form ammonia from urea Primary pyelitis is much less frequent in men than in women Lenhartz[6] in eighty cases had only six in males It is quite frequent in female infants

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Colon Bacillus Septicemia

Cases of generalized infection with the colon bacillus are probably more frequent than is generally recognized As the majority of these cases recover they often pass unrecognized In making this diagnosis the bacillus coli must be obtained from the blood during life as just preceding death entrance of the colon bacillus into the blood current is of quite frequent occurrence

A general infection has its origin most frequently in the gall bladder or the urinary tract rarely directly from the intestinal tract Jacob[14] in a series of 13 cases traced the infection to the gall bladder in 3 the urinary tract in 3 the female genitalia in 3 and the intestinal tract in 3 In the remaining cases the source of the infection was not determined Brian reports 2 cases of colon bacillus cholecystitis complicating typhoid In addition he collected 49 cases from the literature where the source of the infection was fairly accurately determined in the intestine 12 biliary passages 15 urinary system 13 genitalia 9 Three of intestinal origin either followed an acute enteritis or some local infection especially one in the appendix followed by pyelophlebitis

The clinical manifestations are largely those arising from the primary focus It is difficult to differentiate the symptoms arising from the generalized infection from those due to the local process The onset of the generalized infection is often marked by a chill followed by a septic type of fever with leukocytosis of varying intensity Jaundice is often present especially where there is a complicating cholangitis from the gall bladder infection Herpes has been reported in several cases Luger[15] reported a case with signs and symptoms resembling a polyarthritis Coleman and Hastings[16] in 1909 reported two cases of their own and several others collected from the literature of colon bacillus infections closely resembling mild typhoid both as regards onset and symptomatology including in some rose spots and leukopenia It is quite possible that recent methods of diagnosing typhoid would have shown that some of these so closely resembling typhoid were actually cases of this disease

Metastatic infections due to colon bacillus septicemia are on the whole infrequent when compared with pneumococcus or streptococcus sepsis In forty nine cases collected by Jacob metastatic infection was observed in 22 5 per cent In five of these the endocardium was involved Local metastases were present in others in the spleen kidney liver lungs and thyroid There was one case of periostitis

The diagnosis depends upon the detection of the colon bacillus in the blood during life This should not include positive cultures secured when the

drainage from the kidney Kretschmer and Gaarde[11] report eleven cures in fourteen cases treated by this method They employed a one per cent silver nitrate solution using a small catheter so the solution might return down the ureter to the bladder By avoiding rapid distention of the pelvis the irrigation is not painful except that incident to the instrumentation The treatments are repeated every five to six days until the urine is free from pus and the cultures sterile

There is considerable difference of opinion regarding the value of vaccine therapy It still has strong supporters Others deny that vaccines are of any value in this condition When the pyelitis is due to stricture of the ureter stone or tuberculosis surgical measures are indicated

Cholecystitis

Typhoid and colon bacilli are the most frequent cause of gall bladder infections and play an important role in gallstone formation The infection is usually of hematogenous origin The lower portion of the common duct frequently contains colon bacilli but only in exceptional cases do the bacilli reach the gall bladder by direct extension up the duct Naunyn[1] has stated that the colon bacillus is responsible for eighty per cent of the infections in the gall bladder It is possible these figures are rather high but Brian[13] found the colon bacillus more frequently present in infection of the gall bladder than any other microorganism Petersen in fifty operations for gallstones found bacillus coli in pure culture in thirty six and associated with other bacteria in six

The colon bacillus is able to decompose the bile salts and cause a precipitation of cholesterin thus playing an important role in the formation of gallstones Experimentally gallstones have been formed by infecting the gall bladder of animals with the bacillus coli

The treatment of acute cholecystitis consists of rest in bed with local application of heat or cold to assist in enforcing quiet Agents to increase the flow of bile should be of value in improving drainage The only drug of the many advocated that possesses this action is ox bile which may be given in 0 3 to 0 65 gm (5 to 10 grains) three times daily It is doubtful whether this agent is sufficiently active to be of any special value

Drugs administered by mouth do not have a germicidal effect in the gall bladder Hexamethylenamin has been used for this purpose but as formalin is only split off in an acid medium it is valueless in this condition In case the symptoms fail to subside or evidence of empyema develops as manifested by septic temperature and leukocytosis drainage is indicated

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patient is moribund The mortality in thirty seven cases collected by Jacob where positive cultures were obtained during life was 40 per cent The prognosis in a large measure depends upon the character of the primary focus of infection Where this is due to an enteritis or urinary focus the prognosis is good *In empyema of the gall bladder or suppurative appendix* the outlook is bad although some of these recover Judging from the three cases of puerperal sepsis reported by Jacob with a mortality of 33 3 per cent the prognosis here is rather favorable The outlook is in any case more favorable than in septicemia due to the staphylococcus or streptococcus The treatment of this condition is that of the primary focus from which the generalized infection originated

Pneumonia

The literature contains a few cases of lobar pneumonia reported as due to the colon bacillus These have usually been cases of generalized infection developing a pneumonia In the sputum of these cases the colon bacillus has been found but associated with other microorganisms known to cause lung infiltration especially streptococci and staphylococci It is still questionable whether the bacillus coli is ever directly responsible for pneumonia in man

Meningitis

Hartshorn[17] in 1914 collected from the literature thirty four cases of meningitis *in infants due to the colon bacillus* Michael[18] has since reported another case In some the infection follows a pyelitis or cystitis in others apparently it arises directly from the intestinal tract and not infrequently it follows an enteritis The process may be either serous or suppurative and not all cases terminate fatally

Hemorrhagic Septicemia of the New Born (Winckel s Disease)

The bacillus coli is considered the etiological agent *in this condition* It is not possible to say that it is always the cause The condition is characterized by multiple hemorrhages hemoglobinuria and icterus It runs a rapid course often terminating fatally in two or three days

CHAPTER XXIII

BACILLARY DYSENTERY

By BURGESS GORDON

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Definition — Bacillary dysentery is an infectious disease caused by *Bacillus dysenteriae* characterized by inflammation of the large bowel with the sudden onset of abdominal pain tenesmus fever and the frequent passage of liquid stools containing blood pus and mucus It occurs sporadically or in epidemic form and may follow either an acute or chronic course

History

The term dysentery is used often incorrectly in describing an ordinary diarrhea Historical accounts of bacillary dysentery therefore are

The writings of the ancient Greeks and Romans indicated some knowledge of the disease. Significant observations were made by Hippocrates who mentioned particularly that tenesmus and fever with the passage of stools containing blood and mucus were characteristic. He considered that dysentery was different from other diarrheal conditions and the mortality rate was high among children. Hippocrates, in differentiating various dysenteries and mentioning the incidence of age groups, said that "children from 5 to 10 years of age are the more apt to die of dysentery and other ages less so." "All cases of lientery are said to be of a bad character when they are continued and protracted both day and night, and when the dejections are either very crude or black, soft and fetid, for they occasion thirst and determine the fluids otherwise than to the bladder, give rise to ulcerations in the mouth, redness and ephelis of all colors, and at the same time the belly is in a state of ferment and has a foul wrinkled appearance externally (as in sprue). All other varieties of diarrhea without fever are of short duration and mild, for they will cease when washed out or of their own accord (as in Salmonella infection)."

Galen elaborated on the writings of Hippocrates, and Celsus ascribed the condition to ulcers of the interior of the intestine which caused tenesmus, griping and pain near the anus. Other ancient writers, including Archigenes and Aurelianus, dwelled on the "bloody flux" and the loathing for food common in dysentery. While the "bloody flux" was mentioned repeatedly in the early accounts, references to liver abscess are infrequent, suggesting either that amebic infection was rare or that suppuration of the liver was uncommon.

Referring to seasonal incidence, the writings of Hippocrates and Sydenham are in agreement. Hippocrates wrote that "if the winter be dry and northerly and the rain southerly, the summer will necessarily be of febrile character and give rise to dysenteries." Sydenham observed in the London epidemics from 1669 to 1672 that "now as ever the epidemic dysentery set in at the beginning of autumn and declined at the approach of winter." "When, however, the character of the year was of preeminently dysenteric constitution, it attacked a few patients at a time, most perhaps at the beginning of spring, or even earlier if there was a sudden thaw." "At other times men were attacked even at *the end of winter or at the beginning of spring*." Concerning epidemics specifically, Sydenham wrote: "Whatever may be those particles which are mixed with the atmosphere which war against health and which determine the epidemic constitution, it is certain that they have a greater

misleading unless there is some reference to the important characteristic, namely the occurrence of the painful passage of loose stools containing blood and mucus. The word "flux" used in the early writings means a blood tinged diarrheal discharge and is considered as synonymous with the term bacillary dysentery. Classical references are found in biblical times, as for example the father of Publius who lay sick of a fever and a bloody "flux". Paul was called upon to pray over the patient. Recovery occurred and others came to Paul and were healed (Acts XXVIII 8)[1]

Dysentery from the earliest times has been a part and parcel of the development of civilization. The characteristics of the bacillary type are mentioned repeatedly in the historical accounts and it may be assumed without the benefit of laboratory procedures that the bacillary organism was responsible for a high percentage of all dysenteries. The disease was rare among the nomads living in sparsely settled regions but later the frequency increased as peoples gathered together for trading and mutual protection against warring bands. The epidemiological aspects of bacillary dysentery, especially the degree of communicability, are shown in the history of wars. From the Peloponnesian War in 431 B.C. to the end of World War II no major conflict escaped the disease, and in the wake of combat there have been hardships, havoc and many deaths. Some wars were lost or won because of bacillary dysentery. Herodotus told how Xerxes I, King of the Persians, in his third campaign against the Greeks in 480 B.C. suffered defeat principally from the ravages of dysentery. A severe epidemic developed during the siege of Metz by Charles V in 1552. The armies of Napoleon in the Russian Campaign suffered severely from dysentery apparently of the bacillary type, and likewise troops in the Mexican, Crimean, Sino-Japanese and South African Wars were struck down by the disease. During the Civil War in 1861 there were 1,739,135 recorded cases of acute and chronic dysentery with 44,558 deaths among the federal soldiers and presumably many were caused by the bacillary organism. The morbidity in the military prisons was frightful, and it appears that no prisoner escaped dysentery. During World War I in Gallipoli, Mesopotamia, Palestine and Salonika and in World War II on the Western Desert, in Normandy and in various regions of the Middle East, Far East and in the South West Pacific there were frequent outbreaks. Epidemics of bacillary dysentery developing independently of wars have been associated with poverty and deprivation as in Ireland in 1806, 1811, 1821 and 1826, in Africa in 1853 and in Russia in 1865.

in 1917 marked further advances in the knowledge of the dysentery group of organisms. Andrews and Inman[3] in 1919 demonstrated the antigenic heterogeneity of the Flexner group of organisms indicating that V, W, X and Z antigens comprise the antigenic structure of the Flexner strain. Important knowledge was gained from Boyd's analytical data of dysentery strains in India (1932-1935)[4] and the extensive review of the literature during World Wars I and II and previously by Felson[5].

General Considerations

Studies and experiences with diarrheal conditions throughout the world, especially in the Middle East and Far East during World War II, emphasize that diarrheal conditions occur in a variety of diseases and under the various circumstances of environment, incapacitating the health and reducing the efficiency of large groups of workers and at one time or another affecting almost entire populations. Prior to the arrival of the American troops on foreign soil at the beginning of World War II, surveys and tabulations of the diarrhea-dysentery problem as particularly stressed in the British literature indicated a diversity of contributing causes as follows: the excessive intake of food and water, excitement, nervous tension, psychosomatic states, acute gastroenteritis of a non-specific type, pellagra, sprue, pancreatic insufficiency, amyloidosis, allergic reactions of the intestinal tract especially to eggs, wheat, fish and cabbage, hyperthyroidism, tuberculosis, syphilis, kala-azar, achylia gastrica, polyposis, helminthiasis, new growth and the group of acute infections such as epidemic diarrhea of the newborn, virus diarrhea and staphylococcous infection. This impressive list re-emphasized that correct diagnosis requires careful study; it remained only for hard and intimate experience with the dysentery problem to arouse full appreciation of the subject. As the havoc and hazards of diarrheal conditions increasingly became apparent, there also grew among the expeditionary forces the realization that close application of the principles of public health was an important requirement.

With history being repeated, it became evident that outbreaks of bacillary dysentery were the most significant causes of disability of all noncombat casualties, presenting a major medical and sanitary problem[6]. The disease appeared where least expected, at ports of disembarkation, in isolated encampments following battle assignments and during the sojourn for rest and convalescence. Numerous troops were lost for

power of action at the time of their first outbreak than at any time afterwards The earlier the stage the worse the symptoms" Jacobus Bontius who reported the great epidemic in Java in 1628 characterized the dysentery as an ulcerated condition of the intestine with attacks of severe pain and continuous purging at first with mucus and later bloody, purulent discharges Sydenham Morton and Willis in 1668 to 1674 recognized the association of arthritis with dysentery In Sydenham's descriptions the onset of chills possibly an indication to him of the pneumonic form of bacillary dysentery is mentioned

While the seasonal incidence of bacillary dysentery and the occurrence in epidemic form became recognized the exact role of flies was not established until Sir John Pringle just before World War I suspected a relationship Pringle wrote as follows and there is an old observation that such seasons as produced most flies caterpillars and other insects (whose increase depends so much on heat and moisture and consequently on corruption) have likewise been most productive of dysentery Quoting from Holmes[1] Pringle also noted the possibility of contact infection and the infectiousness of dysenteric stools 'in camps the contageon passes from one who is ill to his companions in the same tent and from thence perhaps to the next Rush in 1777 discussed the prevalence of bloody diarrhea in infants and the condition was well recognized in the 18th and 19th centuries but the failure to recognize the correct etiology resulted in a high mortality rate The clinicians in tropical regions notably Johnson Martin Annesley and Billingall who reported their observations in the 19th century have added greatly to the total knowledge of the nature and treatment of bacillary dysentery

Discovery of the organism of bacillary dysentery was reported in Japan by Shiga a pupil of Kitasato in 1898 3 years after Losch an assistant in the clinic of Lichwald in St Petersburg discovered the *Entamoeba histolytica*[1] Shiga applied agglutination tests to bacteria isolated from dysentery stools He found the organism was non motile in type gram negative non lactose fermenting non gelatin liquefying and non pathogenic for animals when given in food but fatal when injected Flexner Strong and Musgrave in the Philippines in 1900 discovered similar organisms in Manila and Kruse in Germany isolated an organism similar to that described by Shiga An important step in the differentiation of bacillary organisms was made in 1902 by Marine and Lentz who reported that the bacilli isolated by Shiga and Flexner and Strong could be differentiated serologically as well as in sugar reactions Duval s descriptions in 1904 and later the work of Sonne in 1914 and Schmitz

limited course were lost for statistical tabulation. As with the studies of incidence, accurate evaluation of chemotherapy was obscured by the lack of adequate control and bacteriological study. Possibly many patients with staphylococcus or salmonella infections diagnosed as bacillary suspects and given the benefit of doubt in treatment would have improved without the use of sulfonamides and thus the evaluation of sulfonamide therapy has not been entirely critical. Likewise any possible evaluation of acquired immunity was difficult to establish, especially in 1944 and 1945, as the increasing effectiveness of prevention became apparent. At war's end bacillary dysentery became a relatively mild phenomenon, limiting possibilities for the study of new therapeutic measures and of prevention and for the opportunity to assemble epidemiological data. Accordingly any description of bacillary dysentery occurring since 194 should not be compared with previous epidemics and experiences. Likewise, a uniform method of reporting cases even in the larger cities of the United States and Europe has not been established with the result that accurate figures are impossible to obtain.

EPIDEMIOLOGY

Bacillary dysentery occurs throughout the world, in cities as well as in rural sections, chiefly in the tropical and subtropical countries where sanitation is inadequate or non existent. It is far more common than amebic dysentery. While bacillary dysentery is a hot weather disease in the subtropical countries such as Egypt, it stops in the hottest weather, corresponding with the disappearance of flies, to reappear as the weather becomes cooler and the flies return. In the tropics, where the bacteria tend to flourish and the people hold no respect for the standards of public health, all of the forces for dissemination are increased. Epidemics in cities occur when the circumstances are particularly favorable as in the squalor of overcrowded sections. Asylums, mental hospitals, nursing homes, prisons, internment camps, boarding houses and ships are the usual sites. It still occurs in epidemic form in cultured northern European countries. In the United States local outbreaks are reported from time to time. All age groups are susceptible, especially young infants and the aged. The disease is largely responsible for the high infantile and child mortality in the tropics. There is a marked acceleration of the disease in civilian populations during pilgrimages and migrations and in war time due to privation, close intermingling

service because of illness requiring other corpsmen to substitute for those who otherwise would have been assigned for duty in new installations for maintenance or combat. While recovery was the rule, prolonged convalescence and recurrence of the condition reduced noticeably the total personnel available for active duty. Also retarding efficiency was the presence of diarrheal conditions among civilians serving in the various installations. Deprived of their assistance, the burden of various unskilled duties fell to the hard pressed corpsmen and others resulting in fatigue and lowered resistance predisposing to disease. Adding fuel to the problem was the presence of unidentified carriers who apparently in normal health were aiding, abetting and perpetuating bacillary infection.

Intensive studies of the stools were made time and facilities permitting especially in hospital centers established for special diagnosis. The causative organism was identified and the type determined whenever possible. However with the expanding campaigns limited transportation and the arrival and speedy deployment of larger bodies of troops, it became impractical to send all patients affected with dysentery to hospitals where adequate studies could be undertaken. With the acceptance of the sulfonamides as specific treatment for bacillary dysentery many patients were given the drugs without benefit of bacteriological study. The criterion of loose evacuations of stools containing blood, pus and mucus with the symptom of tenesmus became recognized. Thus in emergency diagnosis and to some extent by reason of necessity only the unimproved or doubtful cases were sent to general hospitals for detailed study.

Likewise in the local civilian hospitals there was an inclination to discontinue specific or complicated laboratory procedures because of limited personnel and the increasing needs to share equipment in various overtaxed institutions. While unquestionably much was learned during World War II about incidence and epidemiology of bacillary dysentery that previously was not well understood it appears on reflection that the terrific problems of war and mass movement of troops prevented the fullest type of study and evaluation. Perhaps many cases that had been diagnosed as bacillary dysentery without the advantage of laboratory procedures were in fact staphylococcus infections or salmonelliasis and likewise some of the unsuspected cases may have been bacillary dysentery. A particular fallacy in statistical analysis concerned the cases with mild symptoms in patients who were not sick enough to seek medical attention. Undoubtedly numerous mild infections following a self

limited course were lost for statistical tabulation. As with the studies of incidence accurate evaluation of chemotherapy was obscured by the lack of adequate control and bacteriological study. Possibly many patients with staphylococcus or salmonella infections diagnosed as bacillary suspects and given the benefit of doubt in treatment would have improved without the use of sulfonamides and thus the evaluation of sulfonamide therapy has not been entirely critical. Likewise any possible evaluation of acquired immunity was difficult to establish especially in 1944 and 1945 as the increasing effectiveness of prevention became apparent. At war's end bacillary dysentery became a relatively mild phenomenon limiting possibilities for the study of new therapeutic measures and of prevention and for the opportunity to assemble epidemiological data. Accordingly any description of bacillary dysentery occurring since 194 should not be compared with previous epidemics and experiences. Likewise a uniform method of reporting cases even in the larger cities of the United States and Europe has not been established with the result that accurate figures are impossible to obtain.

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of peoples and interference with proper sewage disposal are factors Troops are subject to bacillary dysentery in military advances and during their associations with civilian populations

The means of transmission of bacillary organisms are flies, carriers, food and fingers Fundamentally methods for disposal of feces and the care of the hands, following bowel evacuation are closely involved in transmitting the infection Flies are implicated, especially in tropical countries where other contributing factors also prevail[9] Witness the sleeping servant or workman with flies crawling over his eyelids face and lips and it may be assumed that this person is the potential victim of bacillary infection An important factor in fly-transmission is the degree of viability of the organism It was found that flies will transmit bacillary organisms from dried feces to culture plates for as long as 12 days after passage of the feces In North Africa Stewart[10] reported that the organisms under natural conditions of drying were viable 11 days after passage of the stools While the organisms are easily killed by direct sunlight they may survive for a considerable time in the shade or in the moist ground especially when nurtured in the mucoid type of stools Carriers of the bacilli are not uncommon About 3 per cent of recovered patients may serve as carriers of bacilli for three or more months after cessation of symptoms Epidemics may follow upon the occurrence of mild cases and during epidemics positive cultures may be obtained from as many as 25 per cent of apparently healthy contacts or carriers A certain group of chronic carriers may harbor the infection without appearing sick, some will recall on close questioning the admission of bouts of intestinal cramps with loss of weight and diarrhea The carrier state apparently is influenced by the type of bacillary organism involved as for example it was found in Bengal Province that the Shiga carriers are less common than Flexner carriers but the carrier state persists longer in the former The Flexner carrier usually passes the bacilli more intermittently, discharging bacilli for 3 or 4 days followed by a long interval and a subsequent recurrence

An important factor of transmission by water has been indicated in the positive cultures obtained from floating objects in the jube a canal providing water for the city of Teheran The jube serves conveniently for bathing washing dishes and clothes and becomes at high tide the gateway for the disposal of household garbage At various places the water is circumvented by ditching to houses in order to fill water tanks or pools for use in bathing cooking and for any other purpose, eventually the water returns to the jube for better or for worse Gathering

unto itself debris night soil and the products of defecation of man and animals the stream meanders along becoming a mere trickle the waters appearing almost grossly alive with worms and bacteria The jube is turned off twice daily in order to fill the reservoir during the off period it is customary for animals and children to frolic in the soft muddy bottom adding their share of contamination With the stream turned on there is a holiday spirit people gather on the banks in time to receive the first water the concentrated polutions being washed along for their dubious benefit For those who live at the lower end where the canal becomes a mere trickle and vegetation is negligible and where the mud turns to dust and blows about there is less celebration and perhaps more contamination It is shocking that the population still remains confident in the proverb that flowing water is pure water' Elsewhere in England Germany and in the United States the *Bacillus dysenteriae* has been recovered from contaminated water It is known that chlorination is incapable of rendering contaminated water safe and that organisms survive in water and ice for many weeks

It appears that any food will harbor and transmit *Bacillus dysenteriae* The most frequent outbreaks follow the eating of green uncooked vegetables watered from irrigation ditches to maintain freshness and weight Fruit such as melons and oranges with broken skins on sale in open markets is a common means of transmission in Egypt and Northern Persia Milk has been identified as a medium of transmission the contamination originating from flies and food handlers Curiously meat is more often implicated in outbreaks of Salmonella infection

Various customs and tenets of the population are factors in the dissemination and perpetuation of bacillary dysentery as for example the religious practice of wiping the parts with the bare fingers or the hand following defecation While the fingers are rubbed in dirt or sand afterwards there can be no confidence in this form of cleansing Preparing food for others and eating afterwards must be an important means of dissemination The laissez faire attitude towards the frequency of bowel movements with their softness of composition accepted as natural by the native population but which may contain the *Bacillus dysenteriae* emphasizes the potential dangers of transmission

ETIOLOGY

Bacillus dysenteriae or *Shigella dysenteriae* is the etiological agent of dysentery as proved in the following criteria of activity it is found in

of peoples and interference with proper sewage disposal are factors. Troops are subject to bacillary dysentery in military advances and during their associations with civilian populations.

The means of transmission of bacillary organisms are flies, carriers, food and fingers. Fundamentally, methods for disposal of feces and the care of the hands following bowel evacuation are closely involved in transmitting the infection. Flies are implicated, especially in tropical countries, where other contributing factors also prevail.[9] Witness the sleeping servant or workman with flies crawling over his eyelids, face and lips, and it may be assumed that this person is the potential victim of bacillary infection. An important factor in fly transmission is the degree of viability of the organism. It was found that flies will transmit bacillary organisms from dried feces to culture plates for as long as 12 days after passage of the feces. In North Africa Stewart[10] reported that the organisms under natural conditions of drying were viable 11 days after passage of the stools. While the organisms are easily killed by direct sunlight they may survive for a considerable time in the shade or in the moist ground, especially when nurtured in the mucoid type of stools. Carriers of the bacilli are not uncommon. About 3 per cent of recovered patients may serve as carriers of bacilli for three or more months after cessation of symptoms. Epidemics may follow upon the occurrence of mild cases, and during epidemics positive cultures may be obtained from as many as 25 per cent of apparently healthy contacts or carriers. A certain group of chronic carriers may harbor the infection without appearing sick; some will recall on close questioning the admission of bouts of intestinal cramps with loss of weight and diarrhea. The carrier state apparently is influenced by the type of bacillary organism involved, as for example it was found in Bengal Province that the Shiga carriers are less common than Flexner carriers but the carrier state persists longer in the former. The Flexner carrier usually passes the bacilli more intermittently, discharging bacilli for 3 or 4 days followed by a long interval and a subsequent recurrence.

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TABLE I

CHARACTERISTICS OF MEMBERS OF THE DYSENTERY GROUP OF ORGANISMS

(After Manual of Tropical Medicine Military Medical Manuals W B Saunders Co 1945)

Species	Russell's double sugar	Motility	Lactose	Sucrose	Dextrose	Xylose	Mannitol	Maltose	Dulcitol	Inositol	Indol	Hydrogen sulphide	Litmus milk	MR	VP
			Fermentation Tests												
Shigella dysenteriae	A butt	–	–	–	A	–	–	–	–	–	–	–	A ± to alk	–	–
Sh. ambigua	A butt	–	–	–	A	–	–	–	–		+		A ±	–	–
Sh. paradysenteriae	A butt	–	–	–	A	–	A	(A)	(A)	–	±	–	A ± to alk	±	–
Sh. sonnei	A butt	–	(A)	(A)	A	–	A	A	–	–	–		A clot	–	–
Shigella species Newcastle #	A butt #	–	–	–	A	(A)	–	(A)	(A)		–		A ± to alk ±	+	–
Sh. alkalescens	A butt	–	–	(A)	A	A	A	A	A	–	+		alk	+	–

= Motility questionable Fermentations may produce gas

() = Variable reaction

A = Acid reaction

(A) = Variable acid reaction

A butt = Acid reaction of the butt of the agar slant in the test tube

Alk = Alkaline reaction

MR = Methyl Red

VP = Voges Proskauer

almost pure culture in the stools of dysenteric patients it may be discovered in the stools of healthy persons classified as carriers, it is agglutinated by the serum of dysenteric patients and by the serum of convalescent patients but not by the serum of normal individuals, accidental or intentional ingestion of cultures may lead to the development of characteristic phenomena of the disease

There are three main groups of Genus *Shigella*[11]

1. *Sh dysenteriae*, the Shiga bacillus and *Sh ambigua*, the Schmitz bacillus
2. *Sh paradysenteriae*, the Flexner Boyd types
3. *Sh sonnei*, the Sonne Duval bacillus

The characteristics of *Bacillus dysenteriae* are as follows short rods aerobic or facultative anerobic non motile, with the possible exception of the Newcastle variety measuring 2μ to 3μ by $0{\cdot}6\mu$, negative for gram s stain glucose fermenters without the formation of gas non-lactose fermenters with the exception of *Sh sonnei* which is variable, and prompt growth at the optimum temperature of 37° C, in ordinary laboratory medium forming clear translucent colonies The organisms are killed at a temperature of 55° C in one hour by 0·5 per cent phenol in 6 hours and by 1 per cent phenol in 15 to 30 minutes They resist drying for 20 to 25 days The organisms survive in milk and water for a few days and may live in soil for more than 90 days Table I illustrates certain characteristics of the dysentery group of organisms

Various strains of *Bacillus dysenteriae* are divided according to their action on mannitol (a) mannitol fermenters include the Flexner group of organisms *Sh sonnei*, *Sh alkalescens* and *Sh dispar* and (b) the non mannitol fermenters include Shiga bacillus and the Schmitz bacillus There is an antigenic heterogeneity of the Flexner group of organisms or for example it is known that V W X and Z antigens comprise the antigenic structure of every Flexner strain (Andrewes and Inman[3]) This heterogeneity varies considerably in relative preponderance in a given strain each strain requiring its own anti serum for complete agglutination Subraces are recognized as for example VZ and WX With the Shiga organism there is no production of indol and no hemolysis of red blood cells either of human beings or animals it gives rise to a soluble toxin possibly an endotoxin and when suitably injected produces a powerful antitoxic serum According to Napier[12] the ground up bodies of the Flexner and Sonne bacilli injected into animals are toxic but only in larger doses than in the cases of the Shiga bacillus

ognizes type II a with an antigenic formula of II, 1 3 4 the Roman numerals indicating the specific antigenic component and the Arabic numerals group factors being common to several types Strain X is the degraded result of this type having group components 1 3 4 but containing no specific factor Type II b has the formula of II 1 7 8 whereas the X strains have the same group structure (1 7 8) but are lacking the specific factor Type IV is equivalent to Boyd 103 type V to Boyd P119 and type VI to Boyd 88 Boyd pointed out that his 88 organism has the same antigenic structure as the Newcastle-Manchester bacilli The latter two strains are characterized by the ability to form a very small amount of gas in glucose mannitol and sometimes in dulcitol Otherwise their characteristics are typical of a true bacillary dysentery organism

B Boyd subgroup Boyd also recognized six other *S paradysenteriae* types which reacted very weakly or not at all in sera of the Flexner types These strains (170 P 88 P 74 D1 D19 and D143) have been classified as Boyd types I to VI

TABLE II

SEROLOGICAL CLASSIFICATION OF THE PARADYSENTERY GROUP

(From Manual of Tropical Medicine Military Medical Manual W B Saunders Company Philadelphia 1945

Currently in use by the U S Army and by the British Army

Andrewes and Inman	
Shigella paradysenteriae V	*Bacterium dysenteriae* Flexner I
Sh paradysenteriae W	*B dysenteriae* Flexner II
Sh paradysenteriae X, *Sh paradysenteriae* Y, *Sh paradysenteriae* Z	*B dysenteriae* Flexner III
Boyd's original nomenclature	
Boyd 103	*B dysenteriae* Flexner IV
Boyd P 119	*B dysenteriae* Flexner V
Boyd 88	*B dysenteriae* Flexner VI
Newcastle Manchester	
Boyd 170	*B dysenteriae* Boyd I
Boyd P 88	*B dysenteriae* Boyd II
Boyd D1, Boyd D19, Boyd 143, Boyd P274	*B dysenteriae* Boyd III

Recognizing the pioneer serological work of Andrewes and Inman[1] that the mannitol positive and non lactose fermenting (Flexner) organisms were classified as types V, W, X, Y and Z, Slesinger and Elrod[13] state that this system of classification is being supplanted by more fastidious typing methods. Although a split is evident in the genus *Shigella* on the basis of ability to ferment mannitol, biochemical methods are not satisfactory in determining types encountered. As a result, the serological systems introduced by Boyd[1] and modified by Wheeler[11] have been largely accepted as simple and most logical. Slesinger and Elrod[13] have suggested the following classifications:

A Mannitol fermenters

Shigella

1 *Shigella paradysenteriae* group which includes the Flexner and Boyd subgroups. Members of these subgroups are essentially alike biochemically but serologically distinct.

2 *Shigella sonnei*, similar in many respects to *S paradysenteriae* but ferments lactose slowly, does not produce indol. There are two serological races of *S sonnei* — Phase I and Phase II. This organism is serologically homogeneous showing no antigenic relationship with other Shigella species.

3 *Shigella alkalescens* (ferments xylose, dulcitol and glucose in addition to mannitol. It is antigenically homogeneous but shows cross reactions with the Boyd P274 (Boyd type III) organism. It was formerly considered to be non-pathogenic but it is now believed that it is pathogenic.

4 *Shigella dispar*, late lactose fermenter and indol producer, salicin is not fermented. It is serologically heterogeneous. This organism is not pathogenic.

B Non mannitol fermenters

Shigella

1 *Shigella dysenteriae* or Shiga type, does not produce indol.

2 *Shigella ambigua* or Schmitz bacillus, produces indol.

3 Organisms of Sachs[1] and of Christensen and Gowen[10] which have been described recently.

The *S paradysenteriae* group is subdivided into the following subgroups and types:

A Flexner subgroup. Type I is equivalent to the V strain of Andrewes and Inman, type II to W and type III to Z. Races X and Y are considered as degraded type II (W) forms. Wheeler rec-

ognizes type II a with an antigenic formula of II 1 3 4 the Roman numerals indicating the specific antigenic component and the Arabic numerals group factors being common to several types Strain X is the degraded result of this type having group components 1 3 4 but containing no specific factor Type II b has the formula of II 1 7 8 whereas the Y strains have the same group structure (1 7 8) but are lacking the specific factor Type IV is equivalent to Boyd 103 type V to Boyd P119 and type VI to Boyd 88 Boyd pointed out that his 88 organism has the same antigenic structure as the Newcastle Manchester bacilli The latter two strains are characterized by the ability to form a very small amount of gas in glucose mannitol and sometimes in dulcitol Otherwise their characteristics are typical of a true bacillary dysentery organism

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Sh paradysenteriae Z	
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Boyd P119	*B dysenteriae* Flexner V
Boyd 88	*B dysenteriae* Flexner VI
Newcastle Manchester	
Boyd 170	*B dysenteriae* Boyd I
Boyd P288	*B dysenteriae* Boyd II
Boyd D1 } Boyd D19 } Boyd 143 } Boyd P 74 }	*B dysenteriae* Boyd III

The classification of Shiga as quoted by Holmes[1] is as follows

1 Toxin producing and mannite nonfermenting *B dysenteriae* Representative strain is Shiga Kruse bacillus
2 Non toxin producing and mannite fermenting *B metadysenteriae* Representative strains are Flexner Strong, Y Ohno and Schmitz
3 Lactose-fermenting milk coagulating and variant colony-forming organisms *B paradysenteriae* Representative strains are Kruse Sonne Ohara Mita

The serologic classification of the paradysentery group currently in use in the U S Army is shown in Table II The strains in percentage are shown in an analysis by Boyd in 1940 in Table III

TABLE III

Analysis of , 339 Strains of Dysentery Bacilli Isolated in the Military Laboratories of India in 193 193

(Boyd 1940)

Non mannite Fermenters			
Shiga Kruse			14 3 %
Schmitz			5 5 %
Mannite Fermenters			
A Late Fermenters of Lactose and Saccharose			
Sonne Duval			10 9
Non agglutinable with Sonne Duval sera			1 8
B Non fermenters of Lactose and Saccharose			
V W X Y Z			50 %
103	2 %	1 1	15 %
P 119	1 8		
88	5.0		
170	2 6		
P 288	0 9	3 1 %	
P 274	1.0 %		
D 1	0 9		
D 17	0 1		
P 143	0 %		
Inagglutinable / Not investigated			0 %

From Bacillary Dysentery Colitis and Enteritis (Felsen[5] W B Saunders Company Philadelphia 1945)

Incidence

The incidence of bacillary dysentery varies more or less in direct proportion to the care and thoroughness used in prevention Felson summarizes the problems of the infection among the civilian population in the United States from 1934 to 1938 as follows (1) When unclassified infectious diarrheas are studied carefully the majority appear as dysentery ( ) The reported incidence of bacillary dysentery exceeds that of any other infectious diarrhea (3) While sanitary hygienic measures employed among the civilian population in peace time have greatly reduced the incidence of typhoid fever bacillary dysentery remains widely prevalent

The opinions of Felsen are illustrated in the following figures of the reported incidence of dysenteries and typhoid paratyphoid in the United States in 1933 there were 6 5 reported cases of bacillary dysentery and 30 87 cases in 1943 as compared with the decline of typhoid paratyphoid from 3 349 cases in 1933 to 5 48 cases in 1943 While the unclassified diarrheas showed the high incidence of 17 043 in 1933 in succeeding years the incidence was lower as for example 4 961 in 193 1 484 in 1940 6 93 in 194 Reported cases of bacillary dysentery in New York State were 8 in 1933 1 138 in 19 7 and 1 300 in 1939 The figures by States collected by the U S Public Health Service and reported from 1938 to 1940 indicate a varied incidence as for example In Virginia there were 3 867 cases in 1938 4 306 in 1939 and 1 880 in 1940 and in Mississippi there were 9 679 in 1938 9 445 in 1939 and 9 787 in 1940 States with a lower incidence included Connecticut with 104 cases in 1938 and 86 in 1940 and Indiana with 9 cases in 1938 and 16 in 1940 According to tabulations of cities there has been a relative increase as for example in Philadelphia there were 4 reported cases in 1945 10 cases in 1946 and 16 in 1947[17] The total number of cases of bacillary dysentery in the United States as reported by the U S Public Health Service were 0 644 in 1938 1 3 7 in 1939 and 19 15 in 1940 In parallel with the rising incidence of bacillary dysentery the number of epidemics has increased as for example in New York State there were 27 epidemics in 1936 with a total of 1 100 cases and in 1938 there were 72 epidemics with 3 300 cases The above figures and mortality emphasize the view expressed by Felsen that correct identification and better reporting of cases partly explains the rise in frequency of bacillary dysentery

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(Boyd 1940)

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Mannite Fermenters				
A Late Fermenters of Lactose and Saccharose				
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Non agglutinable with Sonne Duval sera				1 8
B Non fermenters of Lactose and Saccharose				
V W X Y Z				50 2 %
103	7	1 1 %	15 %	
P 119	1 8			
88	5.0 %			
170	.6 %			
P 288	0 9	3 1 %		
P 74	1.0			
D 1	0 9 %			
D 17	0 1			
P 143	0 %			
Inagglutinable / Not investigated				2.0

From Bacillary Dysentery Colitis and Enteritis (Felsen[5] W B Saunders Company Philadelphia 1945)

immediate post war period. In Berlin in 1945 bacillary dysentery was prevalent and likewise in Northern Germany there was an unusually high case mortality. While this is essentially a matter of incidence it may be assumed that mortality rates will be proportional due to deprivation and unsanitary conditions. There has been a fourteen fold increase of dysentery in the Netherlands suggesting that only a fraction of the cases occurring elsewhere in Europe have been reported. The spread of winter dysentery for some years past in the North Sea and Scandinavian countries marks a new development the significance of which is not clear. The number of deaths occurring in India as a result of migration and communal problems never will be tabulated; recent visitors suggest the incidence in some areas has increased thirty times.

Figures on the incidence of bacillary dysentery in the U. S. Army during World War II are shown in the accompanying Table IV. The higher incidence of bacillary dysentery among troops assigned to tropical and subtropical parts of the world (6.89 and 8.98 per 1,000) is striking as compared to the low incidence in the United States (.20 per 1,000). As with the civilian populations in tropical and subtropical countries the incidence is higher than in temperate zones. Extreme precautions in the Army in matters of Public Health undoubtedly were responsible for the comparatively low incidence.

The following percentages were derived from the study of 1 98 stools of American soldiers in the U. S. Army General Hospital in Egypt and were reported by Watts and Tallant[19]

Sh. flexner	53	per cent
S. C. C. enteritides	11	
S. morgani	9	
Sh. paradysenteriae Boyd 88	7.5	
S. schottmuelleri	5.5	
Sh. schmitz	4	
Sh. dysenteriae	3	
Sh. sonnei	3	
S. paratyphi		
Sh. sp.	0.5	
Sh. paradysenteriae Boyd 170	0.5	

Examples of statistical data from U. S. Army installations are as follows. In Panagarh, India in 1944 there were 14 proved cases among 250 personnel of a Station Hospital and 9 cases among 121 native employees complaining of or exhibiting diarrheal conditions. Careful sur-

Definite statistics on mortality are not altogether satisfactory because confusion still exists in many countries and districts as to the cause of dysentery. Actually it was not until 1941 that bacillary dysentery was made a reportable disease throughout the United States. Some statistics would imply there has been an increase whereas in fact more cases are being recognized. This is illustrated in the number of deaths due to intestinal infections as follows: 974 deaths were attributed to bacillary dysentery in 1934 and 1,259 in 1938; 2,037 deaths were attributed to intestinal infections unclassified in 1934; 1,400 similar diagnoses in fatal cases were made in 1938. The significant feature is that deaths from bacillary dysentery are not rare and perhaps with more careful investigations the number would be higher. With infants under 2 years of age there were 17,019 deaths due to diarrhea and enteritis in the United States in 1934 and 14,107 in 1938. A breakdown indicating the number actually due to bacillary dysentery is not available.

The incidence of bacillary dysentery outside of the United States in peace time is subject to great variation and considerable question since the contributing factors are numerous and thoroughness of study and accuracy of reporting generally are inconstant. The incidence unquestionably depends on the habits of the people and the type of country and its weather. Illustrating the incidence in some countries are the following examples: in Siam there were 6,764 cases in 1933 and 2,464 cases in 1937; in Palestine there were 206 cases in 1933 and 211 in 1937; in Denmark 640 cases were reported in 1933 and 1,104 in 1937; 1,372 cases were found in the Belgian Congo in 1934 and 953 in 1936; in Anglo Egyptian Sudan 169 were reported in 1936. Observing visitors to these countries will doubt that such low figures are representative because of the frequency of diarrheal cases seen in villages and thoroughfares. Far more significant are the figures of the League of Nations report indicating 32,938 cases of bacillary dysentery in Poland during 1920, the reports of Red Cross officials in France showing almost 100 per cent incidence among prisoners confined in camps of 10,000 to 15,000 populations and the British reports on the health of the Army in India indicating 13,362 cases from 1930 to 1935. Exhaustive studies and surveys in England, Wales, Ireland, Scotland and Germany show a rising incidence during epidemics, wars and mass shifting of the populations. In India where the monsoons are a yearly occurrence there is a seasonal rise of cases usually reaching epidemic figures.

Stowman[18] concluded from a survey in Europe in 1945 that bacillary dysentery is to be feared even more than typhoid fever during the

veys of employees during a period of three months to locate carriers and regulations for out of bounds areas resulted in the elimination of the disease

The figures of Slesinger and Elrod[1] obtained in a study of 264 prisoners of war in the European theater showed *S paradysenteriae* in 4 cases of 70 per cent of the group examined They also found that most of the Shigella organisms were Flexner types Studies of carriers suggest varied incidence in a group of 65 prisoners of war with shigella infections 3 gave no history of diarrheal attacks of any kind for at least one year prior to the examinations indicating that 8 3 per cent of the entire group were chronic carriers Fairbrother[8] discovered an incidence of 10 per cent in a group of 500 apparently healthy Italian prisoners of war The incidence in Sudanese Indians and Persian food handlers or workmen according to various studies was to 4 per cent of shigella carriers as compared with a much higher percentage of worm infestations Smiley and Raskin[1] state that diarrheal diseases in the Navy have increased since 19

Pathology

Bacillary dysentery causes an acute diffuse inflammation of the mucosa of the colon with the formation of a diphtheritic membrane followed by necrosis and ulceration of the mucosa The pathology of the intestine and the location of the processes vary somewhat with the age of the patient the type of organism the severity of the infection and the stage of the disease While the usual concept of bacillary dysentery is that of a bowel affection there are evidences of involvement of other organs as in the acute toxic cases characterized by necrosis of the liver kidneys and suprarenal glands and congestion of the brain

In adults during the early stage of Shiga or severe Flexner infections there is rapidly spreading hyperemia with catarrhal inflammation of the mucous membrane usually of the sigmoid colon and rectum the cecum and ascending colon being involved less frequently As edema minute hemorrhages and polymorphonuclear infiltration occur there is an extension into the submucosa causing marked thickening of the intestinal wall and inflammatory activity of the lymph nodes Later strips of membrane appear and when removed the underlying ulcers are found on the summits of the intestinal folds with extension into the submucosa and muscularis Perforations are encountered rarely Secondary bacterial infection is observed in the ulcerated lesions associated in the

TABLE IV

NUMBER OF ADMISSIONS AND RATES FOR BACILLARY DYSENTERY IN TOTAL ARMY UNITED STATES AND OVERSEAS AREAS

Rate Per 1 000 Mean Strength Per Year[1]

194 — 1945

Theater	Number of Admissions					Rate per 1 000				
	Total					Total				
	42 45	1 24	1943	1 44	194	4 45	1 24	1 43	1944	194
Total Army	4754	1 44	8935	69 8	68	9	( )	(0	90	0
United States	4387	7 0	38	6	80	0	9	46	16	0
Army Overseas	0367	1174	6553	63 3	6 17	1 90	00	3 88	1 66	1 34
North America	0	10	13	6	1	06	10	07	05	01
Latin America	303	98	75	68	6	9	96	62	9	8
Europe	1562	36	40	500	986	36	43	15	0	4
Mediterranean	3978	21	85	909	196	(8	9	6 24	1 40	6
Africa Middle East	2110	1 4	913	06	67	144	0 51	17 1	15 8	8 98
China Burma India	3901	35	608	1 33	1	8 90	4 00	15 35	10 7	6 89
Pacific Ocean Area	04	(6	661	808	359	1 99	4 48	7	1 84	96
Southwest Pacific	591	1 4	1363	1 4	8 1		44	7 18	88	7
Aboard Transports	67	—	8	39	—		0	37	46	0

NOTE (1) DEPARTMENT OF THE ARMY OFFICE OF THE SURGEON GENERAL MEDICAL STATISTICS DIVISION 16 JANUARY 1948

(2) Preliminary data based in part on sample tabulations of individual medical records and in part on periodic summary reports (WD AGO Form 8 122)

Mild dysentery may simulate ordinary gastroenteritis with the onset of sudden abdominal pain 6 to 10 bowel movements daily and fever of 99 to 100 F vomiting and rectal spasm are uncommon There is little evidence of systemic reaction and the discovery of dysentery bacilli may be the first indication of the infection In the very mild cases the stools appear grossly normal except for their loose consistency and foul odor While blood and mucus usually are not seen in macroscopic examinations red blood cells may be found microscopically The Flexner type of organism usually is present in mild attacks The duration of the attack is to 5 days, the symptoms gradually becoming less disturbing and the movements infrequent Confusion in diagnosis sometimes occurs in cases with localized tenderness of the right lower quadrant of the abdomen simulating appendicitis

In the *moderately severe infection* the onset is sudden with abdominal pain and tenesmus followed shortly by diarrhea Malaise prostration elevated temperature of 100 101 F with headache and foul eructions may precede the gastrointestinal symptoms Straining tenesmus and abdominal pain accompany each bowel movement varying in number from 10 to 30 or more daily The odor of the stools becomes sour or unpleasantly sweet due apparently to the frequent evacuations and the lack of food It was observed in civilian cases in India during World War II that continuation of a fecal odor of the stools indicated *destruction of the intestinal mucosa with putrefactive alterations of blood* in the bowel a serious prognostic sign Signs of dehydration are not uncommon severe rectal prolapse may occur With meningitic and pneumonic forms of onset encountered in America as described by Felsen[3] there may be errors of diagnosis until the onset of frank dysentery occurs

In *severe Shiga infections* the symptoms may be comparatively mild at first chiefly of the diarrheal type and then abruptly the course is characterized by the toxic features of cyanosis extreme pallor lowered blood pressure abdominal distension and vomiting The usual course is 7 to 14 days the fever and constitutional manifestations subsiding before the stools return to normal Following the diarrheal phase there is a tendency to constipation which if not protracted favors the healing of intestinal lesions

The typical stool in the moderately severe type of bacillary dysentery is a brown watery fluid which contains much blood flecked mucus *In the microscopic examinations there is a mixture of cellular* exudate with numerous red blood cells polymorphonuclear leukocytes

development of its chronic condition. In the stage of healing there may be little or no evidence of cicatricial contraction of the ulcers and the mucous membrane appears normal except for polypoid thickening in certain cases. In some instances small retention cysts harbor bacillary dysentery organisms apparently as a forerunner of the carrier state. The Shiga infections cause the most severe lesions and correspondingly the most serious clinical manifestations. In the Sonne and Schmitz infections and the mild Flexner variety the lesions rarely progress beyond the stages of inflammation of the mucous membrane with small or shallow ulcers. Since mortality is low in Sonne and Schmitz infections the findings are noted only in sigmoidoscopic examinations.

Bacillary dysentery infecting the infant or young child may be manifested by catarrhal inflammation both of the small and large bowels. According to Holmes[1] ileocolitis of children and bacillary dysentery in most instances are one and the same disease. A striking feature as pointed out by Felsen is the disproportion between the clinical manifestations and the paucity of intestinal symptoms. In fatal cases the chief lesions of the intestines may consist of lymphoid hypertrophy and hyperplasia with some punctate necrosis and hyperemia of the mucous membrane. Inflammation and necrosis of the spleen, liver and kidneys may be pronounced.

Symptomatology

The incubation period usually is 48 hours although it may be as short as 24 hours or as long as 8 days. In an experimental study by Shaughnessy and co-workers of bacillary dysentery successfully produced in man, the incubation period with few exceptions was not longer than 24 hours. When the dosage of living organisms was sufficient to produce moderate or severe dysentery, the subjects manifested vomiting, cramps sometimes within 12 hours and diarrhea beginning within 18 to 24 hours. Medical histories in Persia indicated marked variations of incubation time among service personnel on leave, the manifestations having developed 26 to 72 hours after visiting native areas and restaurants where suspicions of incrimination ranged from the food itself to lack of fly control and the manner of serving.

The symptoms of bacillary dysentery are classified according to degree as follows: (a) mild in types, (b) moderately severe, (c) fulminating and (d) continued (chronic dysentery).

influences symptoms develop Napier classified these cases as mild forms of chronic ulcerative colitis

In *chronic bacillary dysentery*, which may present itself as an elaboration of recurrent bacillary dysentery there is a history of several bouts of dysentery with periods of quiescence and only the presence at various times of *Bacillus dysenteriae* in the stools indicating that recovery is incomplete As the symptoms persist or recur with greater constancy especially in Shiga infections the patient loses weight and strength and dies in the course of years either from the disease or from some intercurrent or associated infection

The symptoms of bacillary dysentery *in infants* are at first irritability and listlessness with a temperature of 103 to 104 F The stools become soft or liquid and contain mucus with or without blood In severe cases signs of collapse occur in association with high fever extreme toxemia and profuse bowel ejections crying is feeble The mortality rate is high in the severe forms especially in epidemics occurring in hospitals and asylums evidently due to susceptibility and high dosage of a virulent organism

Immunity

Acquired immunity is suggested in individuals with known histories of bacillary dysentery with repeated exposures to bacillary infection in whom there has been no recurrence of symptoms Immunity has been considered as a local phenomenon in which the tissues of the intestinal tract become burned out and can no longer favor the growth of the organism Immunity acquired as an inherited state has not been established There is no proof that protective factors are transmitted from mother to infant since bacillary dysentery will occur in the newborn when exposure takes place

Complications

Apart from the tendency of the untreated cases of bacillary dysentery infection to become chronic the general complications are rare The conditions noted are urethritis arthritis neuritis acute parotitis conjunctivitis intussusception achlorhydria macrocytic anemia and bronchopneumonia Peritonitis has been noted in severe cases perforation of the intestine is rare Severe hemorrhage from the bowel is infre

large mononuclear cells macrophages and clasmatocytes, the latter containing red blood cells that sometimes are mistaken for amebae The pus cells show varying degrees of necrosis The Sonne and Flexner types of organisms are found most frequently in the moderately severe cases and the Shiga organism in the severe cases

The *fulminating form* of bacillary dysentery is marked by an acute and extremely severe onset of profound toxemia with profuse outpouring of fluid from the bowel 50 to 100 movements daily, sometimes containing nothing but blood and pus with vomiting collapse and fever of 103° to 105 F The fulminating type is almost always caused by Shiga infections the overwhelming toxemia being due to the toxins elaborated by the organism In the untreated cases watery bowel movements may last for 1 or 2 weeks and prostration and dehydration become marked resembling cholera, tenesmus is distressing and patients remain on the bed pan almost continuously Sleep is fitful the skin becomes dry the cheeks drawn the mouth parched with herpes on the lips sweating may be profuse the blood pressure may fall to systolic 60 mm of mercury The entire abdomen becomes sensitive to the slightest pressure of the sheets In cases with diphtheritic membrane of the bowel there is severe vomiting with retching pyrexia and symptoms of marked toxemia The abdominal pain and tenesmus may decrease or disappear with the increase of toxemia an unfavorable sign The fulminating type may last 10 to 14 days leaving the patient in a deplorable state of chronic dysentery or more commonly death results

Recurrent bacillary dysentery according to practitioners in the Middle East and Far East is not uncommon among the native populations Characterized by the passage of loose stools containing small amounts of blood and mucus the attacks apparently are due to inadequate treatment of the initial attack The exact frequency is difficult to establish because of the possibility that some occurrences are due to independent or superimposed staphylococcus and salmonella infections which are common in the crowded cities where imperfect food is sold Napier[1] refers to the experience of new arrivals in a tropical country who suffer a succession of mild attacks of dysentery due to reinfection Recurrences continue until the individual has developed a specific immunity to all common strains of *Bacillus dysenteriae* With the severe attacks there is considerable damage to the bowel and while healing may result there always is the tendency to disturbed function such as a failure of absorption in the lower bowel and under adverse dietetic

appendicitis sometimes are confused The medical history is important for establishing the environmental factors the manner of handling raw food and the onset of the present and previous attacks of dysentery with special reference to the presence of tenesmus and the type of stools The results of microscopic and cultural examinations of stools are important In typical cases the presence of mucus blood and pus will be noted with large numbers of polymorphonuclear leukocytes As compared with the stools of amebic dysentery the leukocytes will show marked effects of toxic necrosis and autolysis A common source of error is to mistake macrophages in a bacillary stool for dead amebae Positive cultures are diagnostic

As compared with amebiasis the classical symptoms of bacillary dysentery are the sudden onset with the higher fever greater toxemia and the frequency of fulminating cases amebiasis tends to be a milder infection, and the stools show the motile *Entameba histolytica* containing red blood cells and a preponderance of mononuclears over polymorphonuclears the cellular exudate being less than in the bacillary type The shift of pain from one side of the abdomen to the other often affected by change in the position of the patient is common in bacillary dysentery Periods of remission may be confusing as shown in the sudden development of explosive or fulminating symptoms after or 3 days of mild diarrhea and abdominal discomfort Occasionally the infection is ushered in with pain in the right lower quadrant of the abdomen simulating an attack of appendicitis as tenesmus becomes widespread over the abdomen succeeded by frequent bowel movements the correct diagnosis is suggested

Exceptional cases of bacillary dysentery will present features of cholera with watery bowel movements and little or no blood In cholera tenesmus is uncommon and vomiting which is copious is often free of nausea and retching Dehydration thirst and prostration are severe in cholera with progressive shrinking of the tissues especially the face and extremities The cholera stools at first feculent soon become rice water in appearance and frequent containing small mucous flocculi but no true inflammatory exudate The vibrios may be seen in cholera stools

Other diarrheal conditions that must be differentiated are ulcerative colitis and mucous colitis of unknown etiology salmonella and schistosoma infections tuberculosis of the colon cancer worm infestations staphylococcus infections poisoning by heavy metals heat stroke and marked deprivation of water The history of the types of food ingested is a lead in the diagnosis Salmonella and staphylococcus infections are

quent notwithstanding the extensive lesions of the mucosa and submucosa with the passage of blood and mucus favoring erosion of blood vessels Arthritis mono- or polyarticular in type has been observed in the Shiga infections restoration of function occurring in from 4 to 6 months The symptom triad referred to as Reiter's syndrome, is a combination of arthritis conjunctivitis and urethritis, it may or may not be etiologically related to bacillary dysentery While the syndrome was ascribed by Reiter[3] to a spirochetal infection, Fiessinger and Leroy[4] attributed the condition to *Bacillus dysenteriae* Young and McEwen consider the syndrome as a combination of three recognized complications of Shigella infection Some believe it an infectious condition of etiology entirely different from the preceding assumptions

In the chronic cases there is a tendency to invasion of secondary organisms especially the pyogenic cocci Association of bacillary organisms with amebic infections has been noted in chronic cases, but there is no relationship except from the coincidence of two infections occurring simultaneously Two patients encountered in surveys of civilian personnel in India were found to be carriers of amebic and bacillary organisms and specific therapy directed for the elimination of the amebic infections relieved the diarrheal symptoms without affecting the presence of the bacillary organisms The association of bacillary infection with schistosomiasis and chronic malaria was noted in Egypt, the presence of dietary deficiency in long protracted cases of bacillary dysentery was common in the Persian Gulf area

Diagnosis

The recognition of bacillary dysentery during epidemics is comparatively simple because physicians are alert to the possibility of its presence The condition often is unsuspected in sporadic mild cases with grossly normal stools especially in districts where contaminated food unfavorable water conditions known carriers and chronic cases are infrequent Localities in the United States which would present the background for bacillary dysentery comparable with the Far East are rare and yet this does not exclude the possibility of sporadic cases Differentiation from amebic dysentery salmonelliasis and cholera in the acute forms and from ulcerative colitis and nutritional states in the chronic types is essential It is recognized especially that the symptoms of amebic dysentery may be remarkably similar to bacillary dysentery infection and cholera and

taining 30 per cent glycerin in saline solution carrying stools in containers warmed with hot water bottles is unsatisfactory It was found at the 263rd General Hospital in Calcutta that material selected from the stools gave a high percentage of positive cultures but the use of rectal swabs was more reliable

Technique of securing specimens by rectal swab as recommended by the U S Army [6] and used in the C B I Theater is as follows Swabs are prepared by wrapping cotton tightly around the end of an applicator stick and inserted into a piece of rubber tubing 0 5 cm inside and 0 8 cm outside diameter 10 cm long with one end beveled for about 1 cm The assembled swabs and rubber tubes are sterilized before use Before securing a specimen the swab is passed so that its tips is slightly short of the opening of the beveled rubber tube The surface of the tube is lubricated care being taken to prevent the lubricant from reaching the swab and covering the opening The tube then is inserted through the anal sphincter for about 5 cm after which the swab is exposed by withdrawing the tube or 3 cm The applicator is rotated so that the mucosa of the rectum is rubbed lightly The swab then is drawn back into the tube and both applicator and the tube combined are removed from the rectum If diarrhea is present it is advisable to compress the tube between the fingers as it is introduced

The technique for cultivation and identification as recommended by the U S Army [8] is as follows Inhibitory media that prevent the growth of *Escherichia coli* and permit the growth of dysentery bacilli greatly simplify the culture of the dysentery organisms Shigella salmonella agar and desoxycholate citrate medium are useful for the purpose If feasible the culture plate should be inoculated at the bedside of the patient by rubbing the swab over it immediately upon removal from the rectum The entire surface of the plate should be smeared After 4 hours of incubation dysentery bacilli form colorless colonies up to 1 mm in diameter sometimes larger on S S agar While pure cultures are obtained sometimes it is advisable to make transfers especially from suspicious colonies to different media such as Russell s double sugar agar or Klingler s iron agar Further biochemical and serological tests should be made to identify the type It appears that the Sonne type is more easily cultivated than the Shiga type In complicated cases bacillary dysentery organisms may be grown from specimens of urine Blood cultures are sterile

Agglutinins — Agglutinins develop during the first week of the disease or at the beginning of the second week as the infection begins

especially confusing A helpful feature in differential diagnosis is the rapidity of onset the incubation period of salmonella and staphylococcus infections usually is 4 hours or less while the time interval of shigella infections may extend from one to three days Suggestive of staphylococcus infection is the history of eating custards, pies, cakes puddings, cream puffs and oil dressings

Special Examinations

While blood pus and mucus in the stools are almost always accepted as diagnostic of bacillary dysentery by physicians who treat numerous cases of dysentery in the Middle East Far East and in the United States where cases are relatively infrequent special examinations usually are desired This difference was noted in the first occurrences of diarrhea originating in troop movements in the United States and after arrival on foreign soil The mere discovery of blood pus and mucus in the stools was not considered by medical officers as critical evidence of bacillary dysentery and fundamental studies were undertaken whenever possible

Stool Examinations — The simplest method for direct microscopic examination is to select a small fragment of fresh stool from the bed pan and place it under a glass slide In typical cases the abundant cellular exudate rich in polynuclears some containing red corpuscles with a variable number of red blood cells will be seen While direct examinations are helpful cultivation and identification are more valuable and should be used if facilities are available

Stool Cultures — Cultural isolation and identification of the organisms from the stools should be undertaken at [illegible] day intervals Unlike typhoid positive stool cultures of *Bacillus dysenteriae* may be present at the beginning of the attack which emphasizes the importance of the procedure As demonstrated by British physicians in Egypt and India the care and facility used in handling stools are important for proper investigations Reflecting over the first studies in new theaters of war it now appears that certain negative reports of early cases were due to faulty carriage of specimens to the laboratories and delays in examination Since most dysentery organisms die quickly in the unnatural habitat of the bed pan once the stool is passed the specimen should be examined within minutes after passing Without doubt the most effective plan is to examine the stool in a laboratory located close to the ward If this is impractical the stool should be diluted with a preservative con

Prognosis

Prognosis is influenced by timely diagnosis and the adequacy of treatment Actually the prognosis is now favorable in the majority of cases properly treated Delays in diagnosis with unsatisfactory care may permit irreparable damage to develop in the mucosa of the intestine resulting in a chronic state Susceptibility of different age groups is a factor in the outcome as illustrated in the high death rate among untreated infants and the aged Close communal living may be a serious influence even in the outcome of mild untreated cases as shown in outbreaks in lowly Persian villages during the last war Recognizing the unfavorable influences that often exist in areas affected by epidemics it is remarkable that sulfonamides almost alone even without the benefit of proper care will lead to a favorable prognosis

The outlook in chronic dysentery is difficult to determine inasmuch as intercurrent infections and general conditions may be an influence The occurrence of two or more attacks of bacillary infections superimposed on syphilis chronic malaria worm infestations Pellagra and severe nutritional states will almost always shorten the span of life expected in these conditions It would appear that the majority of uncomplicated chronic cases of bacillary dysentery in the tropics worry along for years with their bouts of diarrhea and symptoms without noticeably shortening the expectancy of life (old age in the tropics is noticeable because of its rarity) Undoubtedly some dysentery infections disappear as though the soil of the intestine no longer favors growth or perpetuation of the organism

Prophylaxis

General measures are important in the control of sporadic cases and for the treatment of carriers Sanitary disposal of feces and proper isolation of the patients are essential Bedding night clothing and dishes should be disinfected by boiling Attendants of the patient should be warned of the danger of contraction of the disease if the proper precautions are not followed While fly control and food protection are matters chiefly for supervision at their source it is essential for attendants to use all precautions to kill marauding flies especially in mess halls latrines and hospitals and handle food only after carefully washing the hands

to subside The titre usually returns to normal levels within three months Serum usually is tested against an agglutinable strain of the Shiga type and several representative strains of the other groups It is found that the Shiga bacillus is well agglutinated by other strains With other types of dysentery bacteria there is a strong tendency to group agglutination Holmes[1] considers that human serum which agglutinates the Shiga organism and also agglutinates other strains usually is an indication of Shiga dysentery Since it appears that serological tests may be of less diagnostic value than the microscopic study and cultures, the latter should be used routinely

Blood Counts — The leukocyte count may be suggestive only in association with other findings the white blood cell count is slightly elevated (10 000 to 15 000) at the onset of the infection and during the course of toxic cases the count tends to be low (3 000 to 6 000) Secondary anemia occurs in protracted or chronic cases

Sigmoidoscopy — Sigmoidoscopic examinations usually are not advised except in the diagnosis of the chronic form The procedure is disturbing and painful to the patient and there is difficulty with acute cases in differentiating between the various types of ulcerations As would be expected the investigations merely disclose an intensely hyperemic mucous membrane with greyish superficial necrosis In recurrent and chronic cases sigmoidoscopy is of greatest value Punctate follicular hyperplasia punctate necrosis and confluent ulceration may be seen if mucosal and general inflammation are not marked An important advantage of sigmoidoscopy in chronic cases is the opportunity to obtain fresh specimens from a particular site of ulceration proliferation or fibrosis for bacteriological study

Roentgenography — Roentgenographic studies are not recommended in acute bacillary dysentery In chronic bacillary dysentery the x ray with the administration of a barium mixture is of value in determining the presence of intestinal spasm Rapid filling of the large intestine with narrowing of the lumen loss of haustrations and sometimes the reduced length of the colon so called lead pipe colon " occasionally are noted The colon may resemble a string of sausages and in certain instances there is a close resemblance to chronic ulcerative colitis Felsen expresses the view that the roentgenogram is less valuable than direct sigmoidoscopy except for the study of localized lesions of the proximal end of the colon Ordinarily the seat of ulceration or fibrosis of the intestinal wall cannot be demonstrated by roentgenology except where there is associated spasm

Prognosis

Prognosis is influenced by timely diagnosis and the adequacy of treatment Actually the prognosis is now favorable in the majority of cases properly treated *Delays* in diagnosis with unsatisfactory care may permit irreparable damage to develop in the mucosa of the intestine resulting in a chronic state Susceptibility of different age groups is a factor in the outcome as illustrated in the high death rate among untreated infants and the aged Close communal living may be a serious influence even in the outcome of mild untreated cases as shown in outbreaks in lowly Persian villages during the last war Recognizing the unfavorable influences that often exist in areas affected by epidemics it is remarkable that sulfonamides almost alone even without the benefit of proper care will lead to a favorable prognosis

The outlook in chronic dysentery is difficult to determine inasmuch as intercurrent infections and general conditions may be an influence The occurrence of two or more attacks of bacillary infections superimposed on syphilis chronic malaria worm infestations kala azar and *severe nutritional states will almost always shorten the span of life* expected in these conditions It would appear that the majority of uncomplicated chronic cases of bacillary dysentery in the tropics worry along for years with their bouts of diarrhea and symptoms without noticeably shortening the expectancy of life (old age in the tropics is noticeable because of its rarety) Undoubtedly some dysentery infections disappear as though the soil of the intestine no longer favors *growth or perpetuation of the organism*

Prophylaxis

General measures are important in the control of sporadic cases and for the treatment of carriers Sanitary disposal of feces and proper isolation of the patients are essential Bedding night clothing and dishes should be disinfected by boiling Attendants of the patient should be warned of the danger of contraction of the disease if the proper precautions are not followed While fly control and food protection are matters chiefly *for supervision at their source it is essential for attendants* to use all precautions to kill marauding flies especially in mess halls latrines and hospitals and handle food only after carefully washing the hands

Prevalence of flies is associated with the spread of bacillary dysentery and it is necessary to destroy the source of flies and use accepted fly control methods such as swatters, fly traps and insecticides. Stables should be cleaned thoroughly and managed in order to eliminate one of the sources of flies. Properly constructed fly traps placed on the sunny side of latrines, kitchens, garbage stations and stables are invaluable. In military installations located near villages where hygienic conditions are poor it is advisable to screen latrines so that flies will not gain access to human excreta. When native labor is employed, latrines should be provided and their regular use properly enforced. Unkept persons should be excluded from clean areas since they are media for attracting and carrying flies to other parts while serving also as personal carriers of the infection. The use of DDT residual spray (5 per cent DDT in kerosene) applied to surfaces on which flies rest is recommended by the U. S. Army. The preparation is remarkably effective not only as an immediate step in the elimination of flies but also in remaining lethal for two or more months. The spray should be applied in the amount of 200 mgm. per square foot or 1 quart per 250 square feet. Screens, walls, ceilings, light fixtures, fly traps and garbage racks may be treated. It is advised that DDT residual spray be applied in pit latrines evenly over fecal contents at the rate of ounces per latrine box hole twice weekly.

In endemic areas special precautions should be taken in the selection and handling of food and water. Supervision should be practiced at the source as well as in the kitchen and dining room. Water must be properly chlorinated and served in clean pitchers, cups and glasses. Precautions in cooking will not suffice unless clean hands serve the food and water. Experience with amebic as well as bacillary outbreaks originating in native restaurants indicate that food usually was properly cooked but improperly handled afterwards, thus defeating one of the purposes of cooking. A single contact with unclean hands may cause a dozen cases of bacillary dysentery. Regulations for kitchen help must include latrine inspections and practices. While known carriers are not to be condoned, it should be realized that the carrier state alone is less responsible for transmission than the improper practices of hygiene. No waiter should serve food after visiting the latrine without thoroughly washing his hands. Instances of faulty latrine customs were found repeatedly and definitely established as the causes of bacillary outbreaks with correction the source was eliminated. All personnel who handle food should be checked frequently as to personal hygiene. In the presence of an epidemic, stool cultures of food handlers and other kitchen personnel

should be made and repeated at 2 or 3 day intervals to detect carriers. Carriers of dysentery bacilli should be removed as food handlers and treatment promptly instituted; then not permitted to return to work for at least 3 months or until 3 consecutive stools are found to be negative by culture for *Bacillus dysenteriae*. Restaurants and lunch rooms failing to observe sanitary standards should not be visited.

It is extremely doubtful if sterilization of raw vegetables with solutions such as potassium permanganate are of value despite the faith and confidence shown by those who permanently live in the area. Actually the fruits and vegetables of fertile Hunan are literally filled with the dynamite of bacillary and amebic infection. With the local custom of soaking fruit to add weight or prevent dehydration, using ordinary contaminated water for the purpose, the widest possible dissemination of the infection is possible. Obviously the practice should be stopped. There is no safe antiseptic that will eradicate contamination under the skin of fruit and sterilization of the skin of fruit is doubtful.

Care should be taken in the proper storage and refrigeration of prepared food. Salads and cold platters made up from left over foods should be avoided. Dishes and kitchen utensils should be washed in warm soapy water and rinsed in boiling water. While drying and during the storage period the dishes should be protected against contamination. During epidemics all precautions should be doubly maintained.

Outbreaks of bacillary dysentery occurring in nurseries will be prevented only with routine and absolutely rigid practices of maintaining cleanliness of all utensils, bottles and furniture used by infants. It should be emphasized that outbreaks may occur in the best of hospitals when least expected and any relaxation of technique and precautions may become disastrous. Utensils should be thoroughly scrubbed and boiled; furniture should be washed with soap and water; efficient fly control is essential; isolation of affected infants is required; sanitary disposal of feces and sterilization of diapers are essential; scrupulous care of hands and clothing of all attendants is necessary.

The search for carriers, particularly food handlers, should be followed closely. Carriers should not be hired to work in kitchens although they may be safer because of regulation than the group of unknown and non regulated carriers who crop up in one capacity or another.

There is a wide difference of opinion as to the value and expediency of vaccines and questions are raised as to the particular effects in certain organisms. Some will cause severe local or general reactions, notably in the case of the Shiga type of organism. The problem of vaccinating an

ignorant population in a widely separated and diversified community would be colossal Vaccine has not been adopted by the U S Army Morton and Engly [8] find some encouragement in the use of bacterio phage

Treatment

The treatment of bacillary dysentery should be systematic beginning with the first indication of the disease, otherwise the course will be prolonged and recurrences possible This applies especially to travelers and the sojourner who make light of attacks of diarrhea, as for example considering the occurrence of gippy tummy as merely a mild phenomenon to be expected one that will pass uneventually With mistaken diagnoses in diarrheal cases many of which are mild bacillary dysentery infections there is always the possibility of developing a relapsing type of the disease eventually a chronic state Realizing that, if the attacks are treated correctly there is the possibility of developing an immunity which is highly desirable in the present state of sanitation in the tropics it becomes essential to follow a carefully planned regime under medical guidance The general treatment is as follows

Rest in Bed — The patient should be confined to bed and advised to rest on either side using one or two pillows under the head rest must be rigidly followed even in the presence of mild symptoms Under no circumstances should patients be permitted to go to the toilet or sit up in bed to eat and drink otherwise tenesmus will occur resulting in the inclination to evacuate unnecessarily The bed pan should be placed carefully under the patient for each bowel movement using pads of cloth or mercerized cotton in case of soreness of the parts

Fluids — Maintenance of proper water balance is important While the period of dysentery may not be reduced the remarkable general improvement following proper hydration emphasizes its value Undoubtedly failures to provide sufficient water to overcome dehydration and acidosis especially in hot weather are partly accountable for the high mortality rate in infants and the aged Illustrating the definite need for adequate water was the frequent and sometimes frightening phenomenon of dehydration of civilians in the Persian Gulf where the temperature rose to 140 F or more The appearance of the skin and features often resembled cholera Native patients affected with bacillary dysentery without benefit of an adequate fluid intake and seemingly

at the point of death often were restored by adequate fluid intake It appeared that adequate fluid almost was as valuable as the sulfa drugs There is no hard or fast rule for the administration of water except that an adequate amount is indicated Care should be taken not to overdo as emphasized in observing a native workman who with remarkable patience and fortitude accepted 9 liters of water poured into him by his native orderly resulting in a bad attack of dilated stomach In hot weather with bowel movements varying between 8 to 12 daily the intake should vary between 5 to 6 liters daily With inability to take fluids orally intravenous injections of normal saline or 5 per cent glucose solution 1 000 c c warmed nearly to body temperature should be given slowly 2 or 3 times daily With circulatory failure special care should be observed in the use of parenteral fluid In this condition plasma transfusions are valuable in supplementing small intravenous injections of normal saline The Murphy drip may be substituted for oral administration if nausea or vomiting is present provided the bowel movements are not provoked by the procedure

Diet — During the acute stage of the disease it is important to withhold solid food providing instead fluids with some nutritional value in regular but small amounts as for instance albumen water rice water weak tea with lactose clear beef or chicken soup and fresh orange juice Milk is not used because of its tendency to aggravate distension and pain some find that milk is disturbing in Shiga infections With improvement the diet may include smooth cereals fruit juices and milk and later custards buttered crackers soft boiled eggs cabbage water milk toast chicken and mashed or baked potato The return to normal diet should be gradual after the disappearance of mucus blood and leukocytes from the feces While vitamin deficiency is not usually a factor in acute dysentery except among native residents of the tropics and the deserts there may be a tendency to it in protracted or chronic cases generally due to failures of digestion and one of the multivitamin preparations should be given Breast fed infants should continue nursing artificially fed infants may continue with the usual formula unless vomiting occurs and then plain water only should be given orally or normal saline parenterally for 1 or   days

Symptomatic Relief — The symptoms of mild bacillary dysentery may not require therapeutic relief other than that obtained by rest hydration sulfonamide administration and sometimes mild sedation Over treatment especially with opium and catharsis may be disturbing and actually harmful It is now recognized that diarrhea represents the

body's effort to free itself of the bacillary organisms and their products and interference with drugs in the accumulation or retardation of the bowel movements is harmful In older practice blood letting and catharsis were recommended Sydenham for instance advocated blood letting for the removal of toxic matter from the blood and catharsis to favor the passage of poisons through the bowel from the blood In observing that tenesmus was increased by catharsis he prescribed opium sometimes in combination with purging Strong opposition to the administration of opium was expressed by Pringle[1] who found that patients reacted unfavorably to the drug While it is accepted that bacillary dysentery is characterized by irritation of the bowel and that cathartics find their action chiefly by the phenomenon of irritation it seems illogical to employ purging In addition, absorption of toxins from the bowel may be increased because of the irritation to the mucous membrane caused by cathartics Equally inconsistent is the administration of opium, which retards intestinal movements and interferes with nature's effort to rid the body of the infection by diarrhea[1] In a sense diarrhea must be regarded as a blessing in disguise and opium may defeat the very purpose of accelerated elimination Supporting this view was the observation of Persian patients with severe infection in whom diarrhea failed to supervene and overwhelming toxemia developed Unquestionably some cases with toxemia and constipation unimproved with chemotherapy will benefit from sodium sulfate 40 to 60 gm given in one half a glass of water every 2 hours for 6 to 8 doses but usually of greater value in such cases and especially in constipation that follows the acute stage is the use of a colonic irrigation of normal saline solution With the advent of the sulfa drugs opium is rarely necessary If absolutely required for severe tenesmus it should be used with strict limitation Intestinal discomfort usually is relieved by flaxseed poultices or a partially filled hot water bottle applied over the abdomen Antispasmodic drugs of the atropine group formerly used for tenesmus largely have been discarded in favor of the hot applications Sedative drugs such as phenobarbital 30 mgm (gr ½) every 4 to 6 hours should be administered to insure relaxation and proper sleep at night Surgical intervention is not customary, acute cases of perforation are managed more effectively with conservative treatment only

Specific Serum Therapy — At first there was interest in the possible value of serum therapy but since the effects of sulfonamide treatment have become established serum receives only second thought The current view is that serum may be used in Shiga infections for supple

menting the action of sulfonamides but the chief reliance should be placed on the drug The recommended dose of serum is 100 000 to 00 000 I U administered intravenously daily until symptoms subside The value of bacteriophage in treatment is inconclusive[8]

Chemotherapy — The treatment of bacillary dysentery including symptomatic relief has changed remarkably since the introduction of the sulfonamides The problems of toxemia and the severe complications common in the untreated cases are now avoided with modern therapy the long list of empirical remedies has been largely set aside The sulfonamides exert a strong specific action on the dysentery bacillus as was demonstrated in all theaters of the War The four drugs of the group most extensively used were sulfathiazol sulfadiazine sulfaguanidine and succinyl sulfathiazol (sulfasuxidine) The latter two drugs of the class of insoluble sulfonamides were introduced in order to maintain a high intestinal concentration of the drug with low concentration in the blood their principal therapeutic action being directed to the fecal content of the intestine The literature indicates extensive studies of the relative effectiveness of the soluble and insoluble drugs and their specific action in the different types of bacillary organisms As yet there are no final conclusions It is established that sulfaguanidine is absorbed to a lesser degree and succinylsulfathiazol hardly at all except in cases of marked ulceration of the intestine Attempting to evaluate the drugs on the basis of their action upon the bacillary organism Hardy Burns and DeCapito[3] found that sulfadiazine and sulfathiazol are effective in Flexner and Schmitz infections and while sulfadiazine will control massive Sonne Duval infections best this drug is inferior to succinyl sulfathiazol in rendering carriers negative Experiences in both civilian and Army Hospitals in India indicated that sulfadiazine is valuable in treating Flexner and Sonne types of bacillary dysentery and that sulfaguanidine is effective in Shiga Kruse dysentery Summarizing their views of the comparative study of sulfaguanadine succinylsulfathiazol (sulfasuxadine) sulfadiazine and sulfathiazol Hardy Burns and DeCapito[3] conclude that all four drugs markedly modify the course of bacillary dysentery Felsen[3] summarizes the status of sulfonamides in suggesting that beneficial effects in varying degrees may be obtained by the use of both poorly and readily absorbed sulfonamide drugs Theoretically at least treatment would be most effective when the absorbable drugs are used generally since bacillary dysentery is a systemic disease with intestinal manifestations On the other hand the non soluble drugs may have a place since a specific local action is desirable Accordingly the com

bined use of soluble and insoluble drugs may gain favor.[7] Equally important as the selection of the drug or drugs is dosage and the need to begin administration as soon as possible.

According to present practices of use and selection the following sulfonamides are recommended: (1) sulfadiazine is the drug of choice for initial treatment of bacillary dysentery; if sulfadiazine is not available, sulfathiazol may be substituted. The oral dose of either drug is 2 gm. followed by 1.0 gm. every 6 hours; (2) sulfaguanadine, although less effective than sulfadiazine, sulfathiazol or sulfasuxadine, has given good results in many cases and should be considered second choice until set aside by critical experience with other insoluble drugs. The dosage is 5.0 gm. every 6 hours or 3.5 gm. every 4 hours, day and night. Chemotherapy should be continued for at least 5 days and should not be stopped until 2 days after clinical recovery is established. If the infection is refractory or in event of clinical relapse or recurrence of positive stools, treatment should be reinstituted. It may be desirable in such cases to combine the use of soluble and insoluble drugs, as for example, sulfadiazine 4 gm. with sulfaguanadine 4 gm. administered during the first 4 hours and then 1 gm. of each drug every 4 hours thereafter for 24 hours and then 0.5 gm. of each drug 4 times daily for 5 days. Parenteral administration of sulfonamides rarely is necessary. With marked toxemia and the absolute inability to tolerate one of the sulfonamide drugs orally, the soluble salt of sulfathiazol or sulfadiazine 0.06 to 1 gm. per kilogram of body weight may be given in normal saline solution intravenously; as improvement occurs oral administration should be substituted.

In the treatment of carriers with sulfonamides Fairbrother[8] used successfully a routine course of sulfaguanadine 6 gm. 3 times on the first day and 3 gm. 3 times daily for 5 days, employing a total dose of 63 gm. In 16 failures the Flexner organism was noted in 12 cases, Shiga in 2 cases and Sonne in 2. Fairbrother found that the majority of the cases responded to the second course of sulfaguanadine.

In general, sulfonamide therapy should not be instituted before steps are taken to maintain normal hydration; it is advisable to give 200 c.c. of water with each dose of sulfonamide in addition to other fluid administration. The recognized toxic properties of the sulfonamides should be kept in mind. With accepted dosage serious reactions are uncommon except in hypersensitive individuals. Regarding the soluble types, it is known that kidney complications are more common than with the use of the nonsoluble drugs, especially in dehydrated patients treated in warm climates. With high fever and profuse sweating normal saline

solution should be given intravenously In the use of the insoluble sulfonamides marked absorption of the drug may occur in the presence of extensive inflammation of the intestinal mucosa tending to cause renal complications as with other sulfonamides For this reason close tabulation of urinary output is indicated with measures of hydration to be used as in the case of the soluble drugs

Renal complications characterized by hematuria and suppression of the urine call for careful management The appearance of mild microscopic hematuria is no indication for discontinuing the drug but with gross hematuria or pain in the flank especially in the presence of diminished urinary output the drug should be discontinued and coincidently adequate fluid replenishment is indicated until the urine output returns to 1 500 c c or more daily To avoid renal complications when it is difficult to insure a daily urinary flow of 1 500 c c or more the administration of alkalinizing agents with the sulfonamides is advisable Large doses of sodium bicarbonate are effective for this purpose the average individual dose should be 6 gm (90 grains) followed by 2 6 gm (40 grains) every 4 hours With suppression of urine catheterization with lavage of the kidney pelvis should be considered

Several antibiotic drugs are being used in the treatment of bacillary dysentery but the results have not been fully evaluated Streptomycin apparently is specific as indicated in the report of the National Research Council[3] and the studies of Pulaski and Amspacher[33] Ross and his co workers[34] used the oral administration of streptomycin in 34 infants and children with dysentery caused by Shigella organisms The dose in these cases was 400 mgm every four hours (4 gm per day) for 7 to 19 days in the active and carrier group In all cases there was prompt disappearance of the pathogen from the stools and untoward symptoms were not observed Aerosporin is also effective but more toxic than streptomycin and sulfadiazine[34] The effects of aureomycin have not been established Penicillin is of no specific value Wegman[35] concludes from clinical experience with antibiotics that for all practical purposes sulfadiazine is effective and still satisfactory as a chemotherapeutic agent

In chronic dysentery the sulfonamides have been employed as in the acute form Sulfaguanidine usually is given in doses of 4 to 6 gm every 8 hours for 4 or 5 days followed by 3 to 4 gm every 8 hours for 5 days Repeating the regimen may prove valuable Various antiseptic solutions including silver nitrate 1 to 3 per cent and Dakin s solution 25 per cent have been used Chineoform (yatren) may be employed in combined oral and rectal dosage the accepted oral dose is 0 5 gm 3 times daily

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and the rectal dose is 3 gm in 200 c c of water[31] The rectal administration usually is preceded by hot saline irrigations, which in themselves are valuable According to Smyly[31] autogenous vaccines are sometimes effective in chronic bacillary dysentery in the following doses The initial dose of the Flexner type is 10 000 000 bacilli with subsequent doses of 100 000 000 given every 4 to 7 days Shiga vaccine should be used cautiously starting with 5 000 000 increasing to the maximum dose of 15 000 000 The opinion of Indian physicians who have had wide experience with bacillary dysentery is that vaccine therapy definitely is of doubtful value in the treatment of chronic cases

At the end of World War II the sulfonamides combined with irrigations of the bowel were taking precedence over all forms of treatment Surgery is indicated only when complete rest for the colon is required or if irrigation fails to reach the ulcerations located at the higher levels, cecostomy will provide rest for the bowel and appendecostomy fulfills the needs for irrigation

Preventive Treatment

Individuals exposed to the infection especially during epidemics may be given one of the soluble or insoluble sulfonamides realizing that their value under such circumstances is not well established Obviously it may be assumed that many exposed cases became infected i e if ingestion of the organisms is a criterion of infection but surely some will not develop the disease Thus proper control studies are difficult to obtain and undue credit to the drug may be given falsely Recommendations to use sulfonamides for preventive treatment should not be dogmatic as would be the case with atabrine in malarial prevention In epidemics sulfonamides may be indicated for persons who have taken food or liquids contaminated with *Bacillus dysenteriae* the administration should be followed with due regard for the possibilities of toxic effects of the drug employed

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CHAPTER XXIV

CHOLERA

By HOBART A. REIMANN

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The word cholera is said to originate from the Hebrew words, choli ra (morbus malus) The Chinese term for cholera is huo luan and the Arabic, duba It is sometimes called Asiatic cholera and in old terms pestilential asphyxia

Cholera is unique among the infectious diseases It resembles the effects of a strong hydrogogic poison and dehydration brought about by the brief presence and growth in the small intestine of varieties of the *Vibrio comma*, which are pathogenic members of the large family of vibrios

History

Cholera probably has existed since prehistoric times It was no doubt, often confused with other severe enteric diseases but its striking epidemiological and clinical characteristics of sudden purging vomiting collapse and death within 6 to 48 hours set it apart more easily than the others As a result references to cholera or to diseases like it can be traced in ancient Chinese, Hindu Egyptian Greek Babylonian and Roman records One of the first descriptions of a disease which probably was cholera appears in the Nei Ching the oldest Chinese medical classic written about 2600 B C [17] Numerous other references appear in subsequent Chinese writings The first reference to cholera in Western civilization is credited to Thucydides in the fifth century before Christ He described an epidemic among the Athenians including his own attack Aretaeus about the middle of the second century A D gave an excellent description of the disease which is valid even today Susruta described cholera in India in the seventh century of our era Numerous other ancient records of cholera exist in south and southwest Asia from whence it spread in repeated pandemic waves throughout the civilized world[5] Somewhat later from the sixteenth to the eighteenth century the English Dutch French and Portuguese who were engaged in Asiatic exploration and conquest encountered the disease and were responsible for spreading it farther Willis in 1670 described what he called dysenteria acuta epidemica in London which may have been cholera

The modern history of cholera begins with the great pandemic of 1817, which apparently started in India spread in all directions reached almost to Europe and lasted 6 years In 1826 India the chief endemic center again seemed to be the source of another pandemic which lasted 11 years and involved much of the civilized world Cholera reached Persia in 1829 and traveled to Europe by land and sea routes across Astrakhan and Russia Europe was attacked in 1831 and by 1832 it reached America carried principally by Irish immigrants landing at Quebec Montreal and probably New York From the eastern seaboard cholera spread along the lines of travel to the south and west affecting the principal cities and populated area of the United States It was during the

outbreak of 1832 that the intravenous injection of salt solution was used apparently for the first time by Latta of Leith

After this outbreak skepticism gradually rose about the supposed origin of the infection from decomposing organic matter and bad air and excrement from patients was suspected as the source In 1849 Stephens of London suggested that cholera was an infectious disease of the intestinal tract

Several more pandemics recurred One lasting from 1846 to 186 appeared to start in India and spread along caravan routes to Persia Russia and by sea among Indian pilgrims to Mecca Other pilgrims infected in Mecca carried cholera to Egypt and Turkey from where it soon spread to Europe and to the Americas It entered the Mississippi valley from New Orleans in 1848 During the outbreak Dr John Snow made his observations concerning the Broad Street pump of London He showed that alvine discharges entering the well at this site were responsible for cholera among persons who drank the water His discovery made only a transient impression and was discredited by many During this period several investigators also saw what undoubtedly were cholera vibrios in the stools of patients

Another outbreak followed similar routes lasted from 1863 to 1875 and included East Africa During this period two waves spread to the United States one in 1867 and another in 1873 which was the last to affect this country In 1870 McNamara clearly defined the importance of dejecta from patients as the source of infection and realized that the disease is spread by human travel American physicians Peters McClelland and Woodworth also favored the microbic origin of cholera and in 1875 an extensive report was published as U S Executive Document No 95 Intravenous injections of salt solution were used in Shanghai in 1875 but because of technical difficulties were not used widely until after Cox s report in 1897

A great pandemic from 1879 to 1884 was supposed to have originated again in India and reached Europe in 1883 through the ports of France Spain and Italy During this outbreak which occurred soon after the opening of the bacteriological era by Pasteur German and French expeditions went to Egypt to study the disease Robert Koch discovered the causative organism in Egypt in 1883 in India in 1884 and proved his results in an expedition with Roux to Toulon in 1884 Even after the demonstration of the cause skeptics persisted especially Pettenkofer who drank a culture of cholera vibrios to show his contempt for the theory of bacterial cause Pettenkofer developed mild diarrhea shortly afterward which because of its mildness was not then admitted to be cholera but it was no doubt a genuine attack Emmerich repeated the experiment and nearly lost his life thereby

Cholera vaccine was used first by Ferran in Spain in 1885 and by Haffkine in India in 1893 The first demonstration of bacterial agglutination with homolo-

The word cholera is said to originate from the Hebrew words choli ra (morbus malus) The Chinese term for cholera is huo luan and the Arabic, duba It is sometimes called Asiatic cholera and in old terms pestilential asphyxia

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[illegible]

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Specific Immunity

[illegible] the response of man to the bacterium probably [illegible] included under the headings of local or general [illegible] or resistance, the existence of [illegible] the gastrointestinal tract, the acidity of the [illegible] factors. Antibodies, agglutinins and [illegible] phenomenon) often can be demonstrated after [illegible] are of little value in diagnosis because of their [illegible] An attack may confer a short period of [illegible] lasting more than a year. Vaccination with [illegible] even weaker immunity. Mice were actively [illegible] with either toxin or with heat killed vibrios as [illegible] called coproantibody, occurs in the [illegible] apparently excreted or secreted [illegible] blood. However, it is demonstr[illegible]

threat to any country at any time if natural or man made catastrophes disrupt the modern order of life

Etiology

Causative Vibrio

Vibrio commas (*Vibrio cholerae Spirillum cholerae* Comma bacillus) may be described as representatives of a group of unstable vibrios which cause cholera. They are probably related to a number of harmless vibrios and belong to the family *Pseudomonaceae* Tribe *Spirileae*. They appear in varied forms according to the environment and culture phase. In the body vibrios usually are in the *form of slightly bent rods 1 5 to 3µ long and 0 4 to 0 6µ broad with a single polar* flagellum (Figs 1 and [A]). They occur singly in short chains and two cells together occasionally form S s. In culture media they may be bacillary but often are short straight rods or coccoid in form (Fig 2[B]) which probably signify bacterial variation. They are actively motile gram negative and form no spores.

Colonies on agar media resemble those of other enteric bacilli. They are opalescent low flat domes grayish yellow in color and from 1 to 2 millimeters in diameter. Some strains cause slight hemolysis in blood agar medium.

Vibrios grow at temperature between 16 C and 42 C but best at 37 C under aerobic and alkaline conditions. Growth occurs at a range of hydrogen ion concentration between 6 4 and 9 6 best between 7 8 and 8. Growth occurs on media too alkaline for many other bacteria which circumstance is of value in the isolation of vibrios. Growth also occurs in simple peptone water. The fermentation of various sugars is variable dextrose levulose galactose maltose sucrose and mannitol may be changed with the production of acid but no gas forms. Lactose dulcitol arabinose and inulin are not affected. Vibrios hydrolyze starch and liquefy coagulated serum. In gelatin stabs a turnip-shaped area of liquefaction forms like an air bubble at the top. Litmus milk seldom is acidified or coagulated. Hydrogen sulfide and indol are produced and nitrates are reduced to nitrites. The red color which develops when sulfuric acid is added to a *culture of V comma in nitrate peptone broth is called the cholera red re*action but similar changes occur with other vibrios and bacteria as well. The *hemolysis caused by certain strains of V comma on blood agar is a hemodigestive* process which differs from the usual type of hemolysis caused by El Tor vibrios and by other bacteria. Hemolysis occurs irregularly in some strains and while some observers believe that no true cholera vibrios cause hemolysis this is not the case. Nonhemolytic vibrios may become hemolytic and hemolytic vibrios can cause cholera.

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The last serious pandemics began in 1891 and in 1902 During the former the great number of victims in Hamburg, Germany, which was supplied with raw river water as contrasted with the few who were sick in a neighboring city whose water was filtered drew attention forcibly to the water borne nature of explosive epidemics not only of cholera but of other enteric diseases as well The outbreak of 1902 usually referred to as the sixth pandemic, involved chiefly the Orient In the Philippine Islands 166 000 cases and 109 000 deaths were re ported from 1902 to 1904 The islands suffered recurrences in 1907 1911, 1913 1935 and 1936 The use of hypertonic salt solution was popularized by Rogers in 1908 Rogers in 1913 was the first to measure the specific gravity of the blood as a guide to the amount of fluid needed in cholera

Less extensive outbreaks involved Europe from 1908 to 1910 especially Russia Cholera occurred during the Balkan War in 1913 during World War I in the armies of southeastern Europe and among Russian prisoners of war in Berlin and Kiel Other small outbreaks occurred but since 1923 no cholera has been recog nized in Europe outside of Russia where 207 000 cases were reported in the Ukraine in 1922 Cholera remains endemic in India South China and the East Indies where localized epidemics recur at intervals The most extensive ones occurred from 1930 to 1934 when it reached as far north as Peiping, and from 1938 to 1939 In May of 1945 an epidemic appeared in Southwest China which assumed alarming proportions especially because of the current war with Japan The outbreak fortunately reached its peak in July and disappeared by September

Cholera in the United States

Several epidemics occurred in North America as offshoots of pandemics from Asiatic sources by way of Europe They are described in detail by Chambers[3] Outbreaks began in 1832 1848 1866 and 1873 as parts of great pandemics and were introduced usually by immigrants from infected European centers Cholera spread to all parts of the country along the usual routes of travel The mortality rate varied in the different outbreaks from less than 5 per cent to 15 per cent of the community During this period Dr Daniel Drake pioneered a plan of public education in the Ohio Valley for the epidemiological control of cholera and its treatment

After the discovery of the cause of cholera and the adoption of quarantine measures cholera has never regained foothold since 1873 During a period of several months in 1911 cholera was detected by medical inspectors on almost every ship arriving from Southern Europe but secondary cases ashore were pre vented by rigid control It is conceivable however that cholera is an everpresent

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disease probably is never air borne Vibrios remain viable on the surface of fruits and vegetables kept cool and moist for 4 to 7 days They survive for 4 or 5 days in damp clothing or when frozen Reports on the survival time of vibrios in water vary greatly Much depends on the amount of organic and inorganic material in the water the presence of other bacteria and of bacteriophage on the temperature and rate of flow In water vibrios may die in 1 day or remain viable for several weeks but are said to undergo changes in virulence and agglutinative reaction

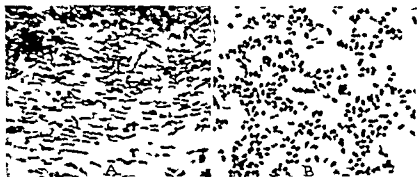


FIG 2 [A] Cholera vibrios other bacteria and detritus in a smear from rectal fluid Vibrios are alined in one direction the so-called fish in stream pattern probably due to enmeshment in a drawnout shred of mucus This arrangement is seen seldom [B] V comma after 1 transfer to agar showing short bacillary and coccoid forms

They are said to survive in sea water It is unlikely except under unusual circumstances that they multiply outside the human body

Classification of Vibrios

Because of the instability dissociation or variability of V *comma* classification is difficult complicated and confusing as in the case of other enteric bacilli Various attempts have been made but none is ideal Heiberg separated 6 types on the basis of fermentation reactions of various sugars Linton and his associates[10] also recognized 6 types based on the basis of component polysaccharides and proteins and of their origin biochemical activities and metabolism The polysaccharides have no relation to immunological reactions nor to the endotoxin.

Classification on the basis of antigenic structure as developed by a Japanese is on firmer ground Kabeshima separated three related types the Inaba the Ogawa and the Hikojima All 3 cause cholera The Inaba type is said to be the most common one encountered the Hikojima the rarest The prevalence of the Inaba and Ogawa types varies in different epidemics and in different places In some Indian epidemics the 2 forms were found together in varying proportions

V. *comma* is comparatively sensitive to adverse circumstances. It is killed in 10 minutes at 55° C and easily by disinfectants. Vibrios are relatively resistant to sulfonamide compounds and to penicillin. Different strains vary greatly in their resistance to streptomycin, some are inhibited by only 2 micrograms per



Fig. 1. Electron micrograph V. *comma* (Anderson and Polevitzky). Plump comma form each with a flagellum continuous with cytoplasm which is shrunken away from the less dense cell wall.

c.c. of broth, others resist 500 micrograms[12]. Vibrios do not survive long in association with ordinary saprophytic bacilli in soil and water. They are killed easily by drying for several minutes. Their sensitiveness to adverse conditions explains why cholera vibrios disappear so quickly in infected communities and why the

In the present confused and unsatisfactory state the grouping in the table based on the antigenic structure of the vibrios in the S phase as proposed by Gardner and Venkatraman and modified by Linton is the simplest available. Further clarification of classification has been proposed by Burrows[1]. Based on the presence of group specific antigen A in vibrios O group 1 he would classify *V comma* according to the combination of group specific antigen with the type specific antigens into 4 immunologic types, namely Type A, Type AB (Ogawa type), Type AC (Inaba type), Type ABC (probably Hikojima type). The eponyms could well be abandoned. Type A represents a new hitherto undescribed type. Two other major antigens D and E are not associated with type specific antigens or with each other and may be used to designate subtypes if desired. There was no immunologic distinction between cholera vibrios and El Tor vibrios. A' antigen does not occur in O groups other than 1.

The instability and variation of vibrios of the cholera group provide clues to many puzzling questions regarding epidemiological and bacteriological behavior. For example, *V comma* in the form in which it causes cholera may, if transferred to resistant persons or for other reasons, dissociate into a nonpathogenic form and as such lose the characteristics by which it may be recognized and identified. In this form it may persist for long periods in carriers or elsewhere until a concatenation of factors again permits it to revert to its typical invasive form to cause disease. This is one explanation at present to account for the perpetuation of cholera vibrios from one epidemic year to another.

Toxin

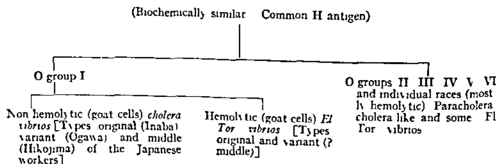
Clinical evidence points to the existence of a powerful toxin or toxic product which is made and set free by *V comma* during its short residence in the intestine during an attack of cholera, yet a true soluble exotoxin has not been isolated. As early as 1895 Pfeiffer and in 1896 Metchnikoff and others caused death of guinea pigs by placing cholera cultures in collodion sacs in the peritoneal cavity. It was later found that *V comma* has ferments which autolyze the cell bodies and set free an endotoxin which causes cholera like symptoms when injected into animals. According to Burrows[9] cholera toxin probably is a dialyzable phospholipid which causes a great increase in the permeability of fluids thorugh isolated strips of intestine. It apparently has an affinity for the

and in others all were of one or the other type In the epidemic at Chungking 1945 all three varieties and one new one were isolated from patients in a small community Epidemics elsewhere have been caused by the El Tor, Celebes and other varieties *Vibrio El Tor* and *V Celebes* vary from other strains and are hemolytic It is safe to predict the appearance and discovery of new types in future epidemics

Into the problem of classification come the complex factors of the somatic O antigen and the heat labile flagellar H antigen The O antigen is specific for *V comma* including some El Tor strains which permits grouping them together as O subgroup 1 as shown in Table I The H antigen is not specific and is shared by many other vibrios For specific

TABLE I

WORKING SCHEME OF CHOLERA GROUP OF VIBRIOS[10]



diagnosis therefore antiserum should contain only O antibody In-agglutinable strains often encountered in epidemics probably represent specific strains which have lost the specific O factor

To complicate classification further *V comma* like other bacteria has smooth S rough R and other culture phases Slight environmental changes or the effect of bacteriophage may induce the S phase to dissociate into the R accompanied by the appearance of bizarre bacterial forms which agglutinate spontaneously in salt solution have no specific O antigen and produce rough surfaced, dry colonies Morphologic changes are striking even in one subculture from the patient s stool to artificial media (Fig 2) It is also possible that one type may change into another Linton Seal and Mitra have induced a new strain to appear by a dissociative process A discussion of the problem is given by Linton[10] For further detailed discussion of classification the reader is referred to textbooks on bacteriology [10 11 3]

in the feces and for a shorter time than is specific antibody in the blood. Its existence in the bowel may account for the short duration of the disease.[9]

Epidemiology

The source of cholera is in a patient with cholera or in a carrier; vibrios are transmitted in the dejecta and infection practically always enters through the mouth. This simple chain of factors makes cholera easier to control than most other infectious diseases. However, so long as there are ignorance, poverty and overcrowding, control is impossible and cholera in endemic centers will persist. When the standard of living improves and brings education, a satisfactory water supply, food control, sewage disposal and a diminution of flies, cholera disappears spontaneously, as it has done in many places. Cholera could be controlled even in a population of low economic status if a few simple rules of hygiene as outlined on another page were observed. But it must always be borne in mind that even in a hygienic community a natural or a man-made catastrophe can easily disrupt sanitation to provide suitable circumstances for an outbreak of cholera if a carrier is present. The control of cholera is more of an economic problem than a medical one.

Cholera is universally thought of as an epidemic disease, but sporadic cases undoubtedly occur and are usually unrecognized as such. Most of the explosive epidemics probably are water-borne, but many others apparently arise simultaneously in widely separated places from other sources and merge to form a pandemic. Local epidemics usually are brief due to the short incubation period, the short, sharp clinical course and the generally short carrier state. Granted that a large epidemic is water-borne from a single source, the perpetuation of it usually is furthered by other means. Epidemics over large areas are spread gradually from place to place by carriers and by contact infection and last for months, usually beginning in June and ending in October in the northern hemisphere. They occur usually in hot weather and are said to be favored by high humidity. In some instances heavy rainfall and floods may cause an epidemic by washing infected alvine discharges into the water supply; in others dry weather and droughts may be the cause by the reduction and pollution of an inadequate water supply (Fig. 11).

Depending on many variable factors, the incidence of cholera in a community varies greatly, ranging from a few cases to [illegible]0 per cent of the population. Among small groups all persons may be attacked.

lining membrane and causes shedding of the epithelium of the intestine and gallbladder. Cholera toxin is feebly antigenic, but antitoxin has been shown by Burrows to have protective properties according to tests in mice.

A substance in filtrates of cultures of *V. comma* has a specific destructive action on the epithelium of the guinea pig's ileum. It is not demonstrable in autolysates of vibrios but seems to be a somatic antigen able to neutralize antibody.

Pathogenicity

Probably because of dissociative changes which occur during artificial cultivation, cholera vibrios are irregularly pathogenic when fed to or injected into guinea pigs and rabbits. Certain strains, when injected intraperitoneally into animals, occasionally cause death of unimmunized animals.

In man the ability of a given strain of vibrio to cause cholera varies greatly, as observed in all epidemics and in the personal experiments of Pettenkofer and Emmerich already mentioned. The same strain may cause rapidly fatal cholera in some persons, severe or mild cholera in others and no disease at all in the rest.

Specific Immunity

Variations in the response of man to the bacterium probably depend on several factors included under the headings of local or general susceptibility, immunity or resistance, the existence of other derangement or disease of the gastrointestinal tract, the acidity of the gastric juice and on other unknown factors. Antibodies, agglutinins and bacteriolysins (Pfeiffer's phenomenon) often can be demonstrated after attacks of the disease but are of little value in diagnosis because of their late and irregular development. An attack may confer a short period of immunity, probably not lasting more than a year. Vaccination with dead vibrios evokes even weaker immunity. Mice were actively immunized by Burrows with either toxin or with heat-killed vibrios as vaccine.

Specific antibody, called coproantibody, occurs in the stools of cholera patients. It is apparently excreted or secreted into the lumen of the intestine from the blood. However, it is demonstrable much earlier

Source of Cholera

The ultimate source of an epidemic has been a riddle for ages Some means must exist by which vibrios are perpetuated from one outbreak to another after intervals of months or years From modern evidence and assuming that man is the only source there are several explanations one is that rare persons serve as carriers who continually or intermittently excrete pathogenic vibrios which under special circumstances may spread suddenly to many susceptible persons another is that vibrios persist in human or other carriers or even outside the body in a dissociated unrecognizable form which under certain environmental circumstances revert to the pathogenic form which we recognize and spread to others a third is that the chain of infection is perpetuated through a continuous series of mild unrecognizable sporadic attacks There is no evidence of sources outside of the human body

Water borne Epidemics — Except along the shore pollution of large reservoirs or lakes or of swift large rivers with incidental great dilution of the inoculum obviously is not as dangerous as that of small ponds and sluggish streams Even then pollution from a single source is apt to be sudden and of short duration Water borne epidemics of this type are explosive and attacks occur simultaneously wherever the polluted water is used The Hamburg outbreak is an example However once the seed is widely disseminated each affected area serves as a secondary focus from which the disease mav be spread more slowly by means to be described

Pollution of small ponds or wells may cause local outbreaks among the few who use the water Water usually is polluted by the discharge into it of dejecta from patients or from carriers or by washing the clothing of such persons in it (Fig 11) Pure water collected from uncontaminated sources may be polluted later bv hands or by filthy containers Vibrios may remain viable in stools and water for several months Cholera may be contracted by swimming in or bathing with polluted water

Other Factors — The fact that outbreaks may occur simultaneously in widely separated places suggests that the presence of carriers and of other means of dissemination at times may be more important than a polluted public water supply as in the case of bacillary dysentery It was the author s impression that this was chiefly the case in the 1945 Chungking epidemic Pure water and clean food may be contaminated easily with fecal matter bearing cholera vibrios especially by hands soiled at defecation by crawling and flying insects and other means Washing vegetables fruit and other food in polluted water keeping them moist with soiled water food plants fertilized with fresh human excrement and eaten raw and shellfish or fish from polluted water are sources of infection Vibrios live in certain foods for weeks or months under favorable conditions

casionally or annually. Sporadic cases occur throughout the year. In India cholera causes from 100 000 to 300 000 deaths annually. In 1944 200 000 cases were reported. Calcutta is the most heavily infected port city. Obviously with conditions as they are in India and in China statistical reports are mere approximations of the actual numbers of attacks. Many unrecognized and unreported cases occur. It is also true that certain other diseases are mistaken for cholera and wrongly included in statistics.

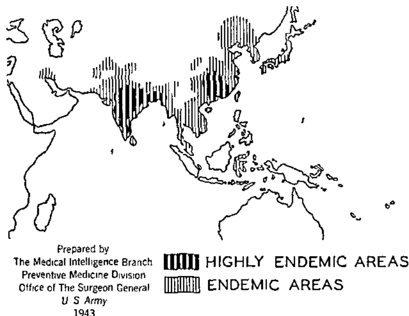


Fig. 3. Present distribution of cholera

A serious outbreak occurred in Formosa in 1943 probably due to the disruption of sanitary regulations by the war. In China the incidence of cholera has increased also because of refugee movements and other martial catastrophes, particularly in South China. An outbreak began in the Yangtze valley in May 1945 which assumed alarming proportions because of the concurrent war. It reached a peak in July and disappeared in September. Sporadic cases appeared until December. An outbreak in the German Army in the Ukraine was reported in 1943.[13]

Pathology

The cadaver of the untreated patient is dehydrated, cyanotic. The skin is shrunken and wrinkled and the cheeks and eyeballs are sunken. The body may

Since vibrios are killed by drying dust is of little or no importance in spreading cholera

Cholera may be transmitted from man to man by hand to mouth infection without the agency of food or water Numerous infections have been acquired in laboratories by deliberately or accidentally ingesting cultures of vibrios

Carriers — If man as is presumed is the only reservoir of cholera *V comma* must persist perennially in some form in the body probably in the intestinal or biliary tract, to perpetuate the infection from one season to the next [11] For vibrios have been encountered in persons in regions where cholera was absent Demonstrable carriers however are rare even in endemic centers during epidemic free periods yet it only takes one shedder of vibrios to start an outbreak Furthermore there has been and still is controversy about the recognition of vibrios as actually pathogenic or potentially pathogenic ones since apparently nonpathogenic vibrios which resemble *V comma* are encountered often The matter is unsettled

In epidemic times carriers are common In different studies from 2 to 20 per cent of healthy persons in contact with the disease temporarily excrete vibrios Of those who have had cholera nearly all 97 per cent no longer shed vibrios in recognizable form after a month but in Greig s experience[14] with Indian pilgrims 30 per cent of those who had the disease still excreted vibrios one of them for 44 days In the author s experience in Chungking in 1945 vibrios could no longer be seen in stained smears from stools in most cases after a week and seldom could be cultivated therefrom after 10 days Obviously the percentage of convalescent and of healthy carriers varies in different outbreaks and in different places Much also depends on the thoroughness of the study and on the bacteriological technic and criteria of identification employed

The healthy carrier, the convalescent carrier and ambulatory patients with mild attacks are often greater menaces in spreading infection than those with severe recognized attacks All of course are dangerous In the Naples epidemic of 1911 90 per cent of patients were said to have been infected by sick and healthy carriers Carriers disseminate cholera as fast as they travel as shown by observations of pilgrims They also account for outbreaks far from the original source Persons who actually are carriers but fail to excrete demonstrable vibrios may be caused to do so by some other gastrointestinal disorder An attack of dysentery for example a dietary indiscretion alcoholic excess or a purgative may evoke vibrios in the stool and may even provoke an attack of cholera

Distribution and Prevalence

Cholera is endemic in southern and eastern Asia Indonesia, Japan (Fig 3) and probably in the Ukraine where epidemics of variable intensity recur oc

Pathogenesis

Only several among a group of persons who ingest V. *comma* may get cholera. Escape from infection is ascribed to acidity of the gastric contents intolerable to vibrios, to other unknown circumstances in the intestine unfavorable to their multiplication, and to specific immunity. Lack of resistance or increased susceptibility undoubtedly are caused by gastrointestinal derangements from other mild or severe infections, cathartics, excesses and probably the harmful effects of malnutrition and vitamin deficiency on the integrity of the mucosa. A vegetarian diet may cause an increased alkalinity of the intestinal contents favorable to the growth of vibrios. These may be considered as predisposing factors. Vibrios which reach the small intestine in susceptible person multiply rapidly over a day or more and for unknown reasons usually disappear within a few more days, too soon to be attributed to the development of antibacterial or antitoxic bodies. Vibrios are found in greatest abundance in the contents of the ileum and can be seen deep in the mucosal crypts, rarely in the tissue. Those seen in tissues locally and occasionally elsewhere are probably there as other particulate matter may be and apparently are not significant. Since vibrios are present only a short time, it may be assumed that the toxic substance liberated by their dissolution is absorbed mostly during the first day or so, and the outcome of the disease is decided at that time. Cholera greatly resembles the effects of an intense hydrogogic poison. A large amount of toxin may cause early death from poisoning; a smaller amount may not be fatal as such but may cause dehydration and uremia severe enough to cause death later. If a patient survives the early shock of acute poisoning and is not allowed to become dehydrated, the chances of recovery are excellent.

The toxin seems to exert its chief effect by greatly increasing the permeability to fluids of the intestinal mucosa without causing inflammation, since there is little or no fever, no pus or blood in the stool and seldom much pain or tenesmus. The copious evacuations gush out like fluid from a massive enema. There is little evidence in most patients of systemic toxemia in the usual sense of the term; the mentality usually is unclouded and recovery is rapid. It is more difficult to account for the massive amounts of fluid which often accumulate in the stomach and are vomited, since vibrios are seldom present in great number there. Perhaps there is regurgitation of fluid from the bowel, or perhaps the transudaton of fluid into the stomach is caused by the effects of circulating cholera toxin on certain centers in the brain or by its direct effect on the gastric lining. Symptoms of cholera can be caused in the rabbit by the intravenous injection of toxin. It is also difficult to explain why no vibrios can be found during intense cholera in certain patients, and why some persons harbor large numbers of V. *comma* without becoming sick.

assume grotesque postures from the intense uneven distribution of rigor mortis which appears shortly after death Weird movements of the extremities are said to occur as a result

The paucity of pathological changes in proportion to the intensity of the disease is characteristic of cholera[1, 2] The findings are chiefly those resulting from a dehydration and a shock like syndrome The absence of inflammatory change is consistent with the view that cholera is essentially toxic in origin The dryness of the viscera so often mentioned in older descriptions is seldom found at necropsy on rehydrated patients At times the serous surfaces may be dry and sticky giving a ground glass like appearance The blood is dark and jelly like

The intestines especially the ileum appear pink from engorgement of the capillaries The lumen holds either clear liquid containing whitish particles of desquamated cells and vibrios or brownish fluid depending on the stage of the disease The solitary lymph follicles of the small and large intestines are swollen from congestion and hyperplasia but Peyer s patches are only slightly affected In Chatterjee s [1] series of necropsies severe changes were present in the wall of the ileum in 30 per cent congestion alone in 20 per cent, and in the rest the intestine appeared to be normal

Microscopically the mucosa of the ileum may be congested degenerated, necrotic or in places denuded of epithelium probably from absorption of 'toxin', but at times simply from postmortem change The crypts may contain myriads of vibrios There is subepithelial edema and intense congestion of capillaries but except for plasma cells there is little or no inflammatory reaction The changes described are found inconstantly Similar changes may be present in the gallbladder Greig found vibrios in the biliary ducts in 80 of 270 bodies The stomach and duodenum are not remarkable but the jejunum may be congested The mesenteric lymph nodes often are swollen contain areas of necrosis and occasionally vibrios

Areas of congestion are found in the liver The spleen may be either smaller than normal normal or slightly enlarged from congestion and hyperplasia of the follicles The normally collapsed capillaries of the bone marrow often are engorged with erythrocytes The thymus often is enlarged Areas of degeneration may be found in the adrenal cortexes There may be areas of congestion or of consolidation in the lungs probably from secondary infection late in cholera Greig found vibrios in the pneumonic areas in some cases

The kidneys show dilation of the glomerular capillaries and intertubal vessels and thickening of the basement membranes Hydropic vacuolization of the tubular epithelium and at times hemoglobinuric nephrosis are seen The histological changes may be insignificant in proportion to the severe degree of functional renal failure

Vomiting often but not always comes soon after the onset Fluid is ejected usually without nausea or retching As much as 8 000 c c (2 gallons) of fluid an amount equal to the volume of blood may be lost in stools and vomitus in a day Such dehydration quickly reduces the secretion of urine often to anuria and leads to a shock like condition called the collapse state Spasms of muscles in part due to hypochloremia particularly of the extremities and abdomen become agonizing Muscles stand out as rigid cords and knots during the cramp Thirst is great but attempts to take fluids may excite further vomiting Uncontrollable hiccough may appear There is pallor or cyanosis The conjunctivas are dry and injected Deafness tinnitus and giddiness occur There is hoarseness or aphonia Pleural and pericardial friction sounds may be audible Jaundice may occur The patient is apprehensive or apathetic but can be aroused easily and is clear in mind Restlessness thirst internal discomfort and cramps are noted The soft parts shrink the cheeks and eyeballs sink and the breath is cool The skin is cool and can be grasped as loose inelastic folds that of the hands is wrinkled as if from maceration There is seldom any fever the temperature usually is subnormal A shock like state with peripheral vasomotor collapse may develop in a few hours from dehydration and probably from toxemia The pulse becomes faster weaker and imperceptible The blood pressure falls and sometimes is unmeasurable Coma and death from collapse toxemia and or dehydration may occur a few hours after the onset more often after the first day or two In those who live longer extreme dehydration and weakness prevent further loss of fluid but anuria persists and as a result acidosis uremia convulsions coma and death follow An erythematous eruption may occur High fever may develop The general picture at this time is almost entirely that of extreme dehydration acidosis and uremia

In those who survive purging and vomiting lessen fluid and food gradually can be ingested and retained the pulse improves blood pressure rises the stool becomes semisolid urine is again secreted and recovery occurs with surprising speed Such patients however may die suddenly probably from emboli as a result of hemostatis and thrombus formation during the disease or from other cause

In rare instances it is said that a violent onset may cause a person previously well to drop suddenly in the street and die before aid is offered Another unusual form occurs particularly in debilitated or senile patients in which death occurs without diarrhea or vomiting supposedly from toxemia alone In such patients however the intestine at necropsy often contains a large amount of fluid

Treated Cholera

The severity of cholera is greatly lessened and its duration shortened by vigorous rehydration provided it is done early enough preferably within a few

The effects of dehydration and demineralization particularly of chlorine sodium and calcium are the same as those which arise from other causes and need not be discussed here The spasms of muscles presumably are due to dehydration and hypochloremia The possible rôle of adrenal insufficiency allergy, anaphylactoid phenomena and histamine in the production of the shock like state of cholera is unknown

Symptomatology

The clinical course of cholera has been the same for centuries[9] Until recently however cholera was classified on clinical grounds into various named forms or stages but it is better to regard it as a group of similar specific entities caused by different but closely related strains of V comma and occurring with different degrees of severity The nature of an attack depends upon many factors such as the number of vibrios ingested the type of vibrio the condition and age of the patient at the time of infection and the care the patient receives An attack of cholera resembles that which follows poisoning with a hydrogogue Controversy persists as to the relative importance of the endotoxin in causing toxemia and of dehydration demineralization and acidosis in the causation of symptoms Pathological changes are insignificant in contrast to the violent clinical course

The *incubation period* varies from 1 to 5 days but usually is less than 3 days Predisposing factors have been discussed on an earlier page

Untreated Cholera

Mild Form — Many people who swallow vibrios are unaffected Vibrios either die from unfavorable conditions in the stomach or intestine or remain viable for a time without causing trouble In a certain number of patients there may be from one to several days of mild sickness with malaise usually without fever anorexia, nausea vomiting and fecal or watery diarrhea which easily is mistaken for gastroenteritis of other cause except that V comma is present in the stool These patients have cholera

Severe Form — In a small proportion of cases the onset is slow with malaise abdominal discomfort and mild diarrhea soon followed by purging These so-called 'premonitory symptoms may be those of cholera itself or may be caused by some other mild derangement of the intestinal tract which precipitates an attack of cholera

In most cases the onset is abrupt with profuse diarrhea first fecal then watery There is seldom much pain straining griping or tenesmus Fluid in large amounts gushes out at frequent intervals sometimes 20 times a day as if from massive enemas Evacuations are followed first by a sense of relief then of prostration

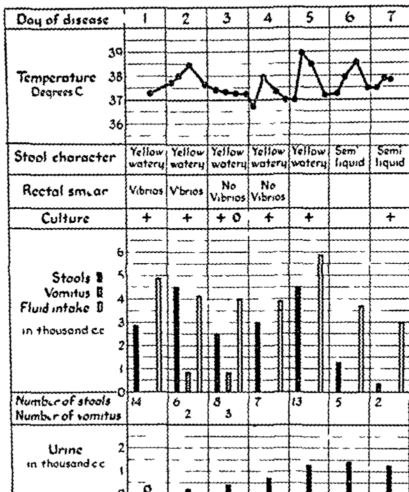


Fig 3 Cholera lasting 6 days Fever probably is caused by injected pyrogenic solutions Continued purging required daily infusions of large amounts of fluid Vibrios *disappeared from smears early owing to experimental therapy with streptomycin but* could be cultivated even on the seventh day The urine volume increased from zero to nearly 1 500 c c on the fifth day

vomiting may cause repeated periods of collapse each of which may be controlled by repeated infusions The fever which so commonly occurs usually is caused by pyrogenic substances in the injected fluid Serious acidosis collapse and uremia seldom occur in properly treated patients When no improvement occurs the diagnosis may be wrong other disease, complication or circumstance

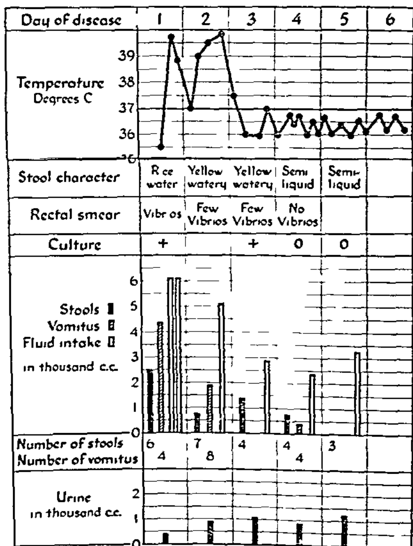


FIG 4. Cholera lasting 3 days. Loss of fluid of nearly 7 000 c c and injection of 12,400 c c on the first day Rapid recovery occurred with diminished loss of fluid and increased urine after rehydration Vibrios diminished after experimental therapy with streptomycin

hours of the onset The injection of adequate amounts of fluid and salts often causes amazingly rapid improvement even during the injection There is often a return to consciousness a filling out of the tissues relief of cramps cessation of diarrhea and vomiting increase of the volume of urine and recovery but the disease may continue for several days (Figs 4 and 5) Continued purging or

of the blood may sink to 7 07 the bicarbonate content to 8 2 the carbon dioxide tension to 16 6 (S H Liu)

The urine is concentrated and contains albumin

Prognosis

Cholera usually lasts from 3 to 5 days ending in death or recovery in this short time Collapse causes about two-thirds of the fatalities uremia the rest The death rate usually is given as from 50 to 70 per cent but it is unlikely ever to be so high except among small groups In large epidemics many mild attacks are not recognized or not diagnosed as cholera and thus escape from inclusion in statistics Among well managed patients the mortality rate should not exceed 8 to 10 per cent[6] In Chungking[1] it was 5 per cent It is unlikely that the mortality rate among large groups will ever be much lower than 5 per cent because of factors mentioned in the next paragraph Cholera when properly treated is a far less serious disease than typhoid

Many factors influence prognosis The death rate obviously is greater in debilitated starved or senile persons when the inoculum has been large in pregnant women and in patients with other disease or complications Different varieties of V *comma* may vary in their pathogenicity In one study vaccination had no effect on the mortality rate as compared with the outcome in unvaccinated patients

Diagnosis

Diagnosis is easy during an epidemic of cholera The sudden onset with purging vomiting cramps anuria and the high mortality need seldom be confused with other disease Yet even during the Chungking epidemic a family suffering from mushroom poisoning was treated at first for cholera In mild attacks and in sporadic cases when early recognition is so important to check an epidemic diagnosis either is not made or cannot be established without bacteriological aid The presence of vibrios in the stained smears of stool is suggestive but not positive evidence Nonpathogenic vibrios exist On the other hand there are numerous unquestioned cases of cholera during which vibrios cannot be demonstrated by stain or culture with careful technic During an epidemic or during the cholera season in an endemic area everyone who has diarrhea should be suspected of having cholera and must be studied bacteriologically The fact that cholera occurs where other diarrheal diseases are prevalent complicates the problem Recognition of early cases and of mild attacks and their proper management is of utmost importance in preventing the spread to others

may be present also or treatment may have been begun too late Among the few patients who died on the author s service two were over 60 years old, one had malaria also and the rest were not treated until several days after the onset or were in a semistarved state

Complications and Sequels

Cholera being so brief has few complications and sequels Pneumonia of mixed infection is the most important complication Gangrene, parotitis bed sores, secondary bacterial invasion in the bowel and corneal ulcers may occur Malaria kala azar dysenteries, typhus typhoid syphilis tuberculosis and other infectious diseases as well as degenerative diseases may coexist with cholera Cachexia from malnutrition avitaminosis mental depression and discontent are common in areas where cholera occurs Pregnant women usually miscarry

Recovery is rapid and complete in most cases but gastrointestinal disturbances occasionally persist for a time Patients who appear to have recovered may die suddenly in certain instances probably from emboli resulting from hemostatis and thrombosis during the attack

Relapse may occur within a few days and because of the short duration of immunity reinfection is possible later

CLINICAL PATHOLOGY

The characteristic stool consists of a large amount of watery clear or slightly turbid colorless or bile stained fluid containing shreds of desquamated tissue looking like water in which rice was cooked It has an albuminous odor Vibrios can be seen in most stools as shown in Fig [A] Linton however, failed to find vibrios in 60 per cent of patients in one epidemic Even if not demonstrable in smears, vibrios usually can be cultivated from stools The vomitus usually is watery bu may contain blood A considerable amount of protein is lost in the dejecta during cholera but no measurements thereof have been recorded

Dehydration causes anhydremia the viscosity of the blood increases and there are erythrocytosis and leukocytosis occasionally with counts of 8 000 000 and 30,000 respectively According to Rogers and Banerjee the lymphocytes are reduced The specific gravity of the blood may range between 1 064 and 1 070 (normal 1 054 to 1 056) in a few patients in the Chungking epidemic it reached 1 076 In severe cases acidosis usually is present the hydrogen ion concentration

that vomiting often precedes painful diarrhea in these Botulism trichiniasis meningitis bacillary dysentery malaria heat stroke and severe deprivation of water at times may cause symptoms resembling cholera Recognition is aided by epidemiological environmental clinical and clinical pathological characteristics of each

TREATMENT

Since prompt and vigorous treatment so greatly reduces the severity of cholera management must be regarded as an emergency measure Treatment begun within a few hours of the onset is most successful Proper treatment can be given easily to individual patients or to small groups of patients when adequate medical and nursing aid and adequate hospital facilities are available However in places where cholera occurs and for the same reasons that it occurs conditions often are primitive Under such conditions a sudden outbreak with hundreds of patients at once makes the care of all but a few impossible and accounts for the high mortality rate Treatment includes the management of the patient and of the epidemic as well

Patients should be cared for in hospitals whenever possible as there therapy and isolation are managed more easily During an epidemic or otherwise patients with mild attacks or those suspected of having cholera should be kept in bed isolated and observed Their excreta should be examined carefully for V *comma* sterilized or properly buried

Treatment should be commenced as soon as possible after a history is taken a physical examination is made a blood count and urinalysis done the pressure and the specific gravity of blood measured and smear and culture of the stool made All data including temperature volume of the stool vomitus and urine and amounts of fluid ingested and injected should be recorded in chart form (Figs 4 and 5) Measurement of the pH of the blood and the carbon dioxide combining power are helpful but facilities for this seldom are available Even if no vibrios can be seen in smears of the stool treatment should be started since reports of cultural studies require several days for completion

Fluids

Water containing 1 per cent sodium bicarbonate should be offered in small amounts every 15 minutes if there is no vomiting but more rapid rehydration and remineralization are urgent in severe attacks Intravenous injection of physiological salt solution warmed to near body temperature should be given at once at the rate of 60 c c to 100 c c a minute in amounts of 1 000 c c to 2 000 c c depending on the size of the patient and the specific gravity of the blood

Bacteriological Methods of Diagnosis

Positive diagnosis can be made by identifying the causative vibrio in the stool or vomitus with the following methods A sample of stool is collected in a clean container or preferably obtained by means of 2 tubes (see Fig 6) inserted in turn into the rectum Material adhering to the outside of a tube is smeared on one or two glass slides fixed stained with dilute fuchsin solution and examined Vibrios when present often appear as those shown in Figure 2[A] They are alined occasionally in parallel which was once believed to be a characteristic Nonpathogenic vibrios may be present in stools and in a certain percentage of patients V *comma* cannot be demonstrated or identified in smears of stools Vibrios if present in forms other than the curved rod cannot be distinguished morphologically from other bacteria

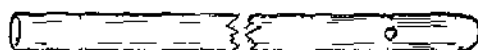


FIG 6 One quarter inch glass tube 7 inches long with a pore near the end The tube is inserted into the rectum drawn gently back and forth to allow fluid to enter the pore and withdrawn for smear and culture

For cultural and serological identification one tube is placed in a test tube containing peptone water and the other in a test tube containing Venkatraman s[16] preservative boric acid sodium chloride medium to which recourse may be had in case of accident to or loss of the first tube culture The test tubes should be sent immediately to an expert bacteriologist The procedure of identification is meticulous and 5 or 6 days are often needed before a final report is ready For details of methods reference should be made to manuals of bacteriology[9, 14, 15] Briefly the peptone water tube is incubated the growth is examined microscopically and tested for agglutination with specific anti cholera serums Alkaline agar plates then are seeded from the culture and suspicious colonies selected later for similar identification tests observing motility and agglutination in antiserums Further identification by the nonspecific "cholera red reaction fermentation of sugars hemolysis of goat s erythrocytes, agglutination with subtype antiserums and the Pfeiffer phenomenon in the guinea pig may be needed If no growth occurs or if the culture is lost the specimen in the preservative medium may be recalled and used for tests

Differential Diagnosis

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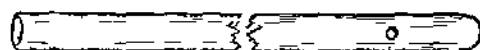


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a deep covered pit remote from any water supply or kitchen Convenient labor saving arrangements for the passage of stools and urine from patients and for their collection are illustrated in Figs 7 and 8 Attendants must be taught



Fig Cholera patient on a fenestrated pallet to facilitate the passage of stools directly into the pot below which contain a 1 per cent solution of cresol A basin for vomitus stands at the left A spike tipped staff driven into the earth supports the infusion apparatus



Fig 8 Method of disposal of excreta after measurement at the bedside The basin is handled with tongs the pot with hooks The bucket is emptied into a deep covered pit behind the hospital Spillage is covered with powdered lime and scooped up

and must observe rigid rules of hygiene Flies and vermin must be excluded by screens and repellants and exterminated with swatters and spray or paint containing DDT or other insecticides

About 300 c c of 2 per cent solution of sodium bicarbonate is added to the first infusion and to subsequent ones if collapse or acidosis are evident Febrile reactions often occur (Figs 4 and 5) from solutions prepared under unfavorable conditions but the urgency of treatment outweighs the dangers therefrom If veins are inaccessible or cannot be entered the intramedullary route of injection into the sternum or tibia may be used

Amazing improvement often occurs rapidly but in many instances purging and vomiting continue collapses recur and require repeated injections sometimes every 3 or 4 hours (Fig 5) Relatively enormous amounts of fluid are needed for cholera As much as 10 000 c c has been infused continuously within the first few hours and more than 14 000 c c in a 24 hour period Injections may have to be given over or 3 days

The specific gravity of the blood must be measured at the bedside, preferably with the copper sulfate droplet suspension technic[11] before sometimes during, and after each infusion and if it is still considerably greater than 1 058 more fluid is needed If actual measurements cannot be made judgment as to the amounts needed must be guided by the clinical response the blood pressure pulse rate, consistency of the blood and the output of urine Care must be taken not to give too much lest overfilling occur warned by restlessness palpitation, substernal oppression cough or edema

Fluids Used — Sterile pyrogen free physiological salt solution 9 gm sodium chloride to 1 000 c c water is the best Some clinicians prefer the addition of 5 per cent dextrose to it but not more than 400 gm of glucose should be given in 24 hours Thiamin chloride 1 mgm for every 5 gm of dextrose, may be added The alkaline solution mentioned contains 6 gm sodium bicarbonate U S P added to 300 c c of boiled distilled water Care must be taken not to cause alkalosis with too much The value of plasma for the shock like state is controversial According to the Army Technical Bulletin[5] the injection of plasma or of blood is useful only for anemia or other special reasons and their injection may be actually harmful However in the experience of a Naval Unit[6] the use of plasma was said to be successful in the treatment and prevention of the shock like state

Routine Care

The management of a cholera patient is otherwise the same as for any severe infection of the gastrointestinal tract Patients should be strictly isolated Clothing bedding and articles they handle should be sterilized by washing with soap and hot water by boiling or with chemicals Alvine discharges and vomitus must be disinfected with 1 to 1 000 solution of mercury bichloride or other germicide before disposal in a sewage system Otherwise they should be emptied into

a deep covered pit, remote from any water supply or kitchen Convenient labor saving arrangements for the passage of stools and urine from patients and for their collection are illustrated in Figs 7 and 8 Attendants must be taught



Fig 7 Cholera patient on a fenestrated pallet to facilitate the passage of stool directly into the pot below which contains a 1 per cent solution of cresol A basin for vomitus stands at the left A spike tipped staff driven into the earth supports the infusion apparatus



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The patient should have a minimum of disturbance During periods of chill and collapse the body should be covered and warmed to normal with hot water bottles or heated coverings Water and liquid or semisolid food may be offered if desired by the patient Restlessness may be treated with barbiturate compounds or with morphine The latter may be used for the severe pain of muscular cramps Complications are uncommon but should be anticipated and treated

Drugs

Since most of the symptoms and signs improve with rehydration and remineralization other drugs are of little value Some of them in common use are harmful Digitalis or other cardiac and circulatory stimulants are not needed unless heart disease itself is present Most of the older medicaments such as purgatives enemas intestinal antiseptics constipating agents opium, specific immune serum bacteriophage and others are of no proved value and are not recommended

Penicillin is of no value The sulfonamide compounds have been used experimentally in their usual dosage but are apparently of not enough value for routine use At best they seem only to shorten attacks slightly However, Chopra[4] reports a mortality rate of 3 8 per cent of 218 patients treated with sulfaguanidine as compared with 6 3 per cent of 94 patients who were rehydrated without the drug Report from a Naval Unit[6] is enthusiastic over the effects of sulfaguanidine and sulfadiazine but the data presented are too meager for final judgment Experience with streptomycin[1] also suggested a slight shortening of attacks but vibrios persisted in the stool It was given in doses of 4 gm orally and 2 to 4 gm parenterally daily for several days

Convalescence

Recovery even without any treatment is often surprisingly rapid but rest in bed should be enforced reasonably for several days Subsequent fatalities may occur suddenly some of them perhaps from emboli Fluid and soft easily digested foods both preferably warm or hot may be offered as soon as desired by the patient Many patients in the Chungking epidemic left the hospital after a week or 10 days Patients should not be released from control until stool cultures no longer contain *V comma*

Management of an Epidemic

The problem is one for prompt vigorous action by public health authorities In endemic areas epidemics should be anticipated before the season of danger

Probably the most effective means to control epidemics at present in primitive regions is by mass education At the onset and during an outbreak the following measures are needed

Elimination of the Source of Infection — Unless the infection already is widely spread communities where cholera is present, should be quarantined although both patients and carriers may already have escaped Trained inspectors should seek and report all patients or suspected patients and carriers All should be rigidly controlled preferably in hospitals Refugees pilgrims and travelers about to leave epidemic areas by foot train boat airplane or otherwise should be detained for a week The stools of each should be searched for vibrios Carriers should be detained until vibrio-free Similar detention and inspection may be applied at places or ports of debarkation The value of mass anticholera vaccination in controlling an epidemic has never been established

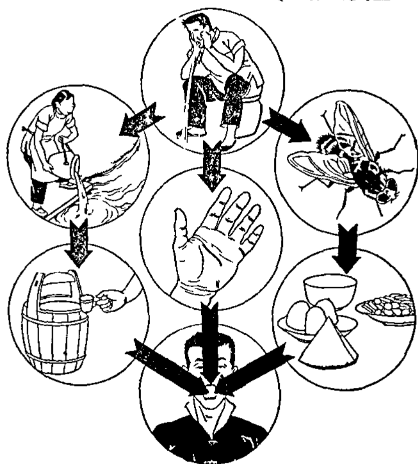


Fig 9 Portion of an emergency cholera hosp tal in a commandeered cinema theater Hastily constructed fenestrated pallets of bamboo a e arranged in 3 rows of 12 beds each for men Women s and children s pallets in equal number are behind the partition to the left Admitting office is in the rear

Food water and handlers thereof must be inspected and serious errors corrected if found Uncontaminated water should be made available Emergency chlorination of water may be necessary but unless it is thoroughly done it i safer to rely on boiling Impoverished people cannot afford fuel for this purpose General sanitation must be enforced by policing under the direction of Health Officials

Hospital Facilities — Immediate provisions are needed for the treatment and isolation of a large number of patients and of carriers and for their detention until the carrier state ceases In areas where cholera recurs annually facilities for care often are organized In places where cholera strikes unexpectedly it

霍亂傷寒痢疾傳染的途徑



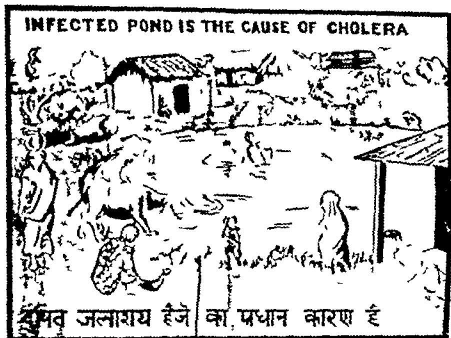
重慶市衛生局印製

預防方法

一 不喝生水
二 不吃露天攤販食品
三 不吃蒼蠅爬過的食物
四 不要和病人接觸
五 要打霍亂傷寒預防針

FIG 10 Poster prepared and distributed by the National Health Administration of China illustrating forcefully and simply how cholera originates how it is spread and contracted

is necessary speedily to evacuate existing hospitals or to organize emergency cholera hospitals in commandeered buildings as illustrated in Fig 9 For the Chungking epidemic health authorities established 10 cholera hospitals with 720 beds within a few weeks Hospitals should be accessible screened and provisions made for advertisement transportation of patients records commissary laundry and sewage disposal Competent medical nursing orderly and laboratory staffs must be hastily organized All should be instructed in the special



POSTER SHOWING HOW A POND CAN BECOME A SOURCE OF INFECTION (INDIA)

圖 解 示 印 度 染 菌 之 池 塘

Fig 11 Poster for natives of India illustrating the dangers of contracting cholera from polluted reservoirs from Wu and associates

problems involved Provisions for bacteriologists technicians and for the preparation of large amounts of fluid for intravenous use are essential For the medical care of 72 patients a staff of at least 6 physicians 10 nurses and 6 orderlies on 24 hour duty in relays is necessary

Educational Propaganda — General education is one of the most important factors in the control of an epidemic[17] It seemed to have an excellent effect in limiting the Chungking outbreak Information and descriptive instruction in

simple language can be broadcast in many ways such as by radio, newspapers, public speakers, school teachers and by illustrated posters placarded throughout the region, especially in the poorer areas. Samples of effective posters are shown in Fig. 10 and 11. The chief advice and information should include the prompt reporting of attacks, the desirability of hospitalization, the location of hospitals and instruction in simple rules of hygiene like the washing of hands after defecation and before handling of food or eating, the proper disposal of dejecta, the eating and drinking of cooked or hot sustenance and its protection from flies, the avoidance of excesses, the destruction of flies and vermin and the avoidance of terror and panic.

Prevention

General. — In epidemic and nonepidemic periods the principles of prevention are similar and are based on the epidemiological facts as already described. The chief points of attack are on the sources of infection in patients and carriers. Their early recognition and isolation are of prime importance as already discussed. Incoming travelers from a cholera region should be quarantined until safe.

General education in personal and public hygiene, modern sanitary plumbing, engineering and water supply, extermination of flies and vermin and abundant properly handled food in themselves automatically eliminate cholera from a community. They all accompany a rise in the living standard and reemphasize that the control of cholera is more of an economic problem than a medical one. Even among impoverished people the observance alone of many simple personal hygiene practices can prevent cholera.

Modern filtration and chlorination systems for safe water are desirable but are expensive long range projects. A chlorine residue of not less than four tenths part per million maintained continuously is said to be necessary, but it is doubtful if that is high enough. Polluted or doubtfully safe water must be boiled and protected from subsequent pollution. Food should be handled cleanly, refrigerated and protected from crawling insects and flies. Flies and vermin may be controlled by screens, traps, swatters and insecticides. Most effective are preparations of DDT which can be sprayed into closed spaces or painted on walls and screens of rooms, latrines and garbage racks. Feces in open latrines should be sprayed with DDT at the rate of 15 c.c. of solution or 8 gm. of dusting powder for each square foot twice weekly. Insecticides superior to DDT are under investigation.

Anti-cholera Vaccine. — The value of specific vaccination for cholera is a matter of continual controversy.[14] It is difficult to arrange controlled tests, but a few careful studies suggest that incidence of cholera is somewhat less after vaccination than without. A recent report by an Advisory Board in India[7]

includes observations on vaccinated and control persons Vaccination with Ogawa and Inaba strains caused cholera to be about 13 times less frequent in vaccinated persons than in unvaccinated ones Immunity was evoked in 3 days and lasted about 5 months There was little difference in mortality rate in vaccinated or nonvaccinated persons who contracted cholera The degree of induced immunity is low and its duration short and this together with its doubtful practical effects makes it unwise to depend alone upon vaccination for immunity Vaccinated persons may have a false sense of security Vaccination often is *necessary to satisfy official quarantine regulations*

Vaccine usually *contains heat killed vibrios of a variety of strains but for* use in a community it is theoretically better to prepare it with the strains which are present locally Initial vaccination consists of 0 5 c c followed in 7 to 10 days by 1 c c given subcutaneously Restimulating doses of 1 c c are given every 3 to 6 months depending upon the apparent need

Personal Prophylaxis — The most important and simple factor is not to eat or drink anything which is not known to be safe or which has not been boiled or thoroughly cooked Sterilized food and drink may be infected later by flies by hands soiled with feces by placing them in soiled containers or by washing or mixing them with polluted water or ice Vegetables like lettuce celery or seafoods should never be eaten uncooked in endemic areas When the available water is under suspicion it must be boiled When boiling is impossible chlorine or other disinfectants may be added Bottled beverages are safe Fruits vegetables and dishes may be sterilized by soaking in a compound germicidal rinse[6] 1 unit in 32 liters (8 gallons) of water Vigilant supervision of the operations of native Asiatic servants and cooks and of their health is necessary Vaccination has been discussed

Fatigue and excesses of any kind must be avoided Overindulgence in alcoholic beverages and minor derangements of the gastrointestinal tract caused by purgatives dietary indiscretion and infections increase susceptibility to cholera A complete diet is desirable to maintain what is called resistance

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CHAPTER XXV

UNDULANT FEVER

By LT. COL. ERNEST P. GENTRY, MEDICAL CORPS, U. S. ARMY

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INTRODUCTION

Synonyms — Malta fever Mediterranean fever simple continued fever Gibraltar fever rock fever melitococcie melitensis septicemia goat fever Texas fever Rio Grande fever Brucella fever

Definition — A general infection caused by one of the sub species of *Brucella melitensis* In man it is characterized by a fever of indefinite duration running an irregular course with a marked tendency to repeated relapses profuse sweats constipation enlargement of the spleen at times by metastatic involvement of the joints and generative organs in the chronic cases by secondary anemia often of severe grade and multiple neuritis Convalescence is protracted and mortality low

In certain domestic animals as cattle sheep goats and swine it is characterized by slight and often unrecognizable constitutional symptoms in the female by a tendency to repeated abortions followed at times by chronic endometritis with subsequent sterility and often by the establishment of a carrier state through chronic infection of the udder with excretion of bacteria in the milk In the male chronic vesiculitis or epididymitis may persist

Historical

The history of undulant fever is unusual For many years students of infectious diseases have recognized two apparently unrelated specific infections occurring in distinct fields undulant fever in man and infectious abortion in animals It remained for Evans[1] in 1918 to demonstrate the extremely close relationship existing between the organisms causing the two diseases This observation has been confirmed repeatedly and has resulted in new concepts of these infections

Undulant Fever in Man — This undoubtedly has existed from very early times Hippocrates briefly describes certain fevers in Thasus which apparently are instances of the disease and gives the history of a case[2] which terminated fatally after 1 0 days During the 18th and early part of the 19th centuries medical officers of the British Army and Navy recorded the occurrence of continued and remittent fevers in Malta and other Mediterranean stations but the disease was not differentiated from associated disorders such as typhoid and malaria In 1859 however Marston[3] wrote an accurate and detailed account of the disease as it existed in Malta terming it Mediterranean remittent or

gastric remittent fever" He described the clinical features of the disease, clearly differentiated it from the existing typhoid fever and established it as a definite clinical entity Veale in 1879 gave an excellent description of the fever as it existed in military patients invalided to England from Mediterranean stations He emphasized the frequency with which rheumatic symptoms occured in patients from Malta and Gibraltar, as contrasted with patients from Cyprus, and clearly differentiated the fever from malaria He recognized the disease as a specific fever, although unable to state its true nature or cause and, in recognition of its complex symptomatology, he suggested it be designated febris complicata

In 1886 Bruce[6 7 8] in Malta discovered in stained sections of the spleen of a patient dead of Malta fever enormous numbers of minute cocci which he was able to cultivate from the splenic pulp of a second fatal case He described the morphological and cultural characteristics of the organism and proved its etiological importance by experiments upon monkeys The micrococcus subsequently was isolated repeatedly from spleens of fatal cases and also from the splenic pulp aspirated during life In 1893 Bruce[9] termed the organism Micrococcus melitensis and in 1896 Hughes[10] urged that the disea e be designated as undulant fever A diagnostic advance of far reaching importance was made in 1897 when Wright[11] and his associates demonstrated specific agglutinins in the blood sera of Malta fever patients

The importance of the disease as a cause of invalidism in the British military and naval forces stationed in Malta led in 1904 to the appointment of a commission by the Admiralty War Office and the Civil Government of Malta under the supervision of the Royal Society for the investigation of the source of the infection in man and if possible to establish measures for prevention The Commission[1] in an exhaustive series of investigations and experiments conducted during the years 1904–7 demonstrated that the infecting organism was frequently present in the milk of apparently healthy goats and that goat s milk was the chief source of human infection in Malta The organism was found to be excreted also in the urine of man and goats and was capable of retaining its vitality outside the body for long periods Prophylactic measures based on these findings promptly resulted in the almost complete elimination of the disease from the British military and naval forces an achievement which constitutes one of the most brilliant triumphs in the history of preventive medicine With the diagnostic aid furnished by the specific agglutination test and the demonstration of the goat as a chronic carrier of the infection endemic centers of undulant fever were reported rapidly from various widely separated parts of the world the earlier distribution of the reported disease being mainly in tropical or sub-tropical countries In 1912 Negre and Raynaud[12] demonstrated an

atypical strain of the organism which they designated as Micrococcus para melitensis

Infectious Abortion in Animals — Epidemics of abortion in domestic animals have existed since the dawn of history An early reference to the disease occurs in the Scriptures[14] where Jacob tells Laban This twenty years have I been with thee thy ewes and thy she goats have not cast their young Orosu[1] tells of an epidemic in Rome in 78 B C of such widespread prevalence that it was known as the Abortus Epidemicus and attacked not only pregnant cows but also women Toward the latter part of the 18th century there are repeated references to the occurrence of enzootic abortion among cattle in various parts of Europe

About the beginning of the 19th century Lawrence[16] and Skellet[17] in England noted the growing belief in the contagious character of the disease In the Complete Farmer[18] published in England in 1807 occurs the following significant advice concerning enzootic abortion It is considered certainly contagious and when it happens the abortion should be immediately buried and the cow kept as widely apart as possible from the herd and not receive the bull that goes with them This belief became so widespread that in 1886 it was proposed in the British House of Commons to bring the epidemic abortion of cattle under the Contagious Disease (Animal) Act[19] The infectious character of the disease was established definitely first by Franck[20] in 1876 when he produced abortions by placing in the vaginas of pregnant animals portions of fetal membranes discharged after an abortion

Nocard[1] in 1885 noted inflammatory changes in the fetal membranes and conducted the first bacterial investigations of the disease He observed two different kinds of bacteria a micrococcus and a short thick bacillus but came to no definite conclusions as regards their etiological importance It remained for Bang and V Stribolt[22] in 1895 to demonstrate for the first time the causative organism From the thick yellowish exudate found present between the uterus and the fetal envelopes in an infected cow they isolated in pure culture a very small Gram negative bacterium designated as the abortion bacillus which they were able to cultivate on artificial media They produced abortion in a pregnant cow by injecting cultures of the organism into the vagina and again recovered the organism from the exudate between the uterus and chorion of the aborting cow By sheep experiments it was demonstrated next that abortion bacilli could be introduced into the pregnant uterus through the blood stream abortion initiated and similar results were obtained in pregnant mares The bull was considered as a probable carrier of the contagion among cattle Bang's work was confirmed in 1902 by Preisz[23] in Hungary and in 1909 in England by M Fadyean and Stockman[24] The latter workers introduced into the diagnosis of the disease the agglutination complement fixation and abortin tests

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Khaled in Egypt Zeller in Germany and Burnet in Tunisia Meyer and Shaw[33] in 1920 proposed that the abortus-melitensis group of organisms be given separate rank as a new genus to be called Brucella after Bruce the discoverer of the Micrococcus melitensis

In 19 1 Bevan[34] in South Africa reported cases of undulant fever in patients in whom the only possible source of infection was from contact with infected cattle The sera of both patients and cattle agglutinated B abortus in high dilution but the infecting organism was not isolated In 1924 Keefer[35] in Baltimore reported the first proven human case of undulant fever caused by the abortus organism in a patient observed by him in the Johns Hopkins Hospital in 1922 Orpen[36] in 19 4 also reported a proven case of abortus infection in a patient in South Africa In 1926 Carpenter[37] isolated the abortus organism from the blood of a case of undulant fever and an identical organism from the cow s milk consumed by the patient With the human strain he produced abortion in pregnant heifers and again recovered the organism from the milk and placentas In recent years numerous cases of undulant fever due to the abortus organism have been reported from various parts of the world

Geographical Distribution

For many years undulant fever was considered to be a disease limited to the Mediterranean littoral Certain definite endemic centers were recognized as Malta and Gibraltar but the fever was reported also from practically all countries bordering on this sea The discovery of the specific organism by Bruce the development of the specific agglutination test by Wright and the recognition of the goat as a source of infection for man gave a tremendous impetus to the recognition of the disease in all parts of the world It was reported soon from South Africa Arabia India China Philippine Islands Southwestern United States Mexico West Indies and portions of South America All obscure fevers in goat raising countries were subjected to specific tests for undulant fever with the result that many positive cases were recorded

A similar extension of our knowledge of the distribution of this disease is now being witnessed as the result of the discovery by Evans of the close relationship between Brucella melitensis (Micrococcus melitensis) and Brucella abortus (Bacterium abortus) together with the demonstration that the latter organism known as the cause of infectious abortion in cattle and swine is also pathogenic for human beings Undulant fever in man due to Brucella abortus has now been reported from the United States Denmark England Holland Germany France South Africa Canada Italy Switzerland Poland Spain Sweden New Zealand and the Dutch East Indies

In 1910 MacNeal and Kerr[5] isolated the specific organism from cattle in the United States and gave it the name of Bacillus abortus, by which it was known for some years. In 1911 Schroeder and Cotton[6] made an important discovery. During a series of 217 milk inoculations into guinea pigs, they found a small bacterium present in 14 per cent. of the milk samples obtained from apparently healthy cows which produced lesions in the guinea pigs resembling tuberculosis and suggested that the organism might be pathogenic for man. They did not identify the organism at first, erroneously considering it to be Gram positive, but shortly afterward Mohler[7] demonstrated it to be the Bacillus abortus. Similar findings were arrived at independently in 1912 by Smith and Fabyan[8] who inoculated B. abortus into guinea pigs and produced a disease with characteristic lesions, from which the specific organism could be isolated. They also called attention to the possibility of human infection. In 1913 Zwick and Krage[9] demonstrated B. abortus in the milk of a cow which had aborted fourteen days previously. The organism then was inoculated into the udders of two goats, producing a severe chronic mastitis with excretion of bacteria in the milk for months without change in its appearance. In 1914 Traum[30] isolated B. abortus from an aborted swine fetus, and in 1916 Good and Smith[31] in the United States first demonstrated that infectious abortion in swine was caused by this organism. They isolated B. abortus from the fetus and fetal membranes, reproduced the disease in pregnant sows and again recovered the infecting organism from the aborted fetuses.

The first suggestion of a relationship between undulant fever in man and infectious abortion in animals occurred in 1914. Kennedy[3] in England, while testing goat's milk for specific agglutinins for the Micrococcus melitensis found, to his surprise, that the cow's milk used as a control gave a positive reaction. Of twenty-two cows subsequently investigated, three gave positive reactions in milk and blood sera to the M. melitensis. Kennedy, however, attributed his findings to a melitensis infection in the cows, and the outbreak of the World War prevented his further investigation of the subject.

New and important fields for investigation were opened up in 1918 by the discovery of Evans[1] in the United States that the Micrococcus melitensis causing undulant fever in man and the Bacillus abortus causing infectious abortion in animals could not be differentiated morphologically, biochemically, culturally, or by the ordinary agglutination tests. She was able to separate the two organisms only by agglutinin absorption tests. Evans at this time made the following prophetic statement: "Considering the close relationship between the two organisms and the reported frequency of virulent strains of Bact. abortus in cow's milk, it would seem remarkable that we do not have a disease resembling Malta fever prevalent in this country." The work of Evans soon was confirmed by Meyer and his associates in the United States,

shown repeatedly that ordinary serological tests cannot be relied upon to distinguish the various species of Brucella By agglutinin absorption tests however Br paramelitensis and certain strains of Br melitensis may be identified and separated from Br abortus The different varieties of Br abortus porcine and bovine cannot be distinguished by serological tests In 190 Feusier and Meyer[11] studied the agglutinin absorption reactions of fourteen strains of Brucella including bovine abortus human melitensis and paramelitensis and found that the strains fell into four serological groups In 19 5 Evans[13] extended this study using 68 strains of Brucella from human caprine bovine porcine and equine sources By the use of agglutinin absorption tests she was able to separate the species into at least eight serologic groups classified as follows —

Groups I II and III — One strain each from bovine and porcine sources Geographical origin United States and Germany

Group IV — Brucella melitensis variety abortus — A large group of 33 strains including the majority of the bovine and porcine strains also 5 human strains Geographical origin one strain each from Austria Holland and Switzerland 30 from the United States

Group V — Brucella melitensis variety melitensis A — A group of 12 strains of human bovine caprine and equine origin Geographical origin United States England Algeria Italy and Tunisia

Group VI — Brucella melitensis variety melitensis B — A group of 7 strains of human and caprine origin Geographical origin Malta and Tunisia This is the organism formerly called Micrococcus melitensis

Group VII — Brucella melitensis variety para abortus — Group of 7 strains of human and caprine origin Geographical origin Sicily and Tunisia

Group VIII — Brucella melitensis variety paramelitensis — Group of 6 strains of caprine and human origin Geographical origin Malta and Tunisia

In the above classification it will be noted that the grouping is not always related to the animal source of the strain and that Group VI VII and VIII prevalent in Mediterranean countries did not occur outside of those regions Ross[46] however has reported recently that of 8 Rhodesian strains of human origin 6 were identified serologically as variety abortus and 2 as variety para abortus Eyre[41] Duncan[41 47] and Bassett Smith[41] feel that too much weight should not be attached to separation into species by absorption of agglutinin tests

Morphology of Organism

A short non motile pleomorphic rod with many coccoid forms measuring usually 0 4–0 6 microns in thickness and varying in length from 0 6–1 5 microns It does not form endospores It stains well with the ordinary aniline dyes but

Etiology

Nomenclature and Classification

The specific bacterial agent of undulant fever now is generally known as Brucella melitensis although bacteriologists are not yet in complete agreement as to details of classification Bruce[6] who discovered the infecting organism in 1886 described it as a micrococcus and for many years it was known as the Micrococcus melitensis Durham[18] in 1898 described it as a cocco bacillus In 1895 Bang and V Stribolt[20] isolated the etiological agent of infectious abortion of cattle which they described as a minute bacillus, although they noted the presence of many coccoid forms This organism was known subsequently as the Bacillus abortus and later as Bacterium abortus In 1912 Negre and Raynaud[13] discovered that a certain strain which was morphologically and culturally indistinguishable from the Micrococcus melitensis, differed distinctly in agglutination and absorption of agglutinin tests To this strain they gave the name of Micrococcus paramelitensis It was found subsequently to be a strain originally isolated by Bruce in Malta To Evans[1] in 1918 belongs the credit for first pointing out the very close morphological cultural, biochemical and serological relationship between the Micrococcus melitensis of Bruce and the bacterium of Bang Evans findings have been confirmed fully by many observers In 19 0 Meyer and his associates[33] suggested the formation of a new genus in the family of Bacteriaceæ to include both the undulant fever and infectious abortion organisms under the name Brucella in honor of Bruce the pioneer worker in the field To this general designation Evans[19] has added the specific name melitensis and the designation Brucella melitensis has been adopted widely Under this nomenclature Micrococcus melitensis becomes Brucella melitensis variety melitensis and Bacterium abortus becomes Brucella melitensis variety abortus The latter has been divided also into bovine and porcine types Huddleson[40] designates the three main varieties of the organism as Brucella melitensis Brucella abortus and Brucella suis according to their respective preferences for caprine bovine and porcine hosts, but he points out that a strain cannot be classified merely on the basis of the animal host from which it has been immediately isolated

It must be stated however that Eyre[41] still classifies Bruce s organism as a micrococcus He finds the bacillary forms only in old or slowly growing cultures and considers them to be either involution forms or the natural elongation of the coccus prior to division Bergey[4] places Bacterium melitensis in the genus Alcaligenes as does also Kelser[43]

Serological Classification —Since the demonstration by Evans[1] of the close relationship existing between the melitensis and abortus organisms, it has been

licle develops In litmus milk the only change is a slight alkalinity On potato there is a slight glistening growth of a brownish color with the pigmentation usually more marked in the melitensis strains None of the usual sugars are fermented In broth cultures there is a fairly definite and characteristic reduction of the H ion concentration equal to about 0 7–0 8 pH In nitrate broth usually no reduction of nitrates to nitrites occurs and indol is not produced in Dunham s peptone solution

An important biochemical reaction which serves to distinguish Br abortus from Br melitensis and Br paramelitensis has been described by Huddleson Hasley and Torrey[51] They have shown that in cultures grown aerobically on rich media containing organic sulphur such as Stafseth s[52] infusion agar beef liver medium (pH 6 6) Br abortus rapidly liberates free hydrogen while Br melitensis and paramelitensis do not The value of this reaction has been confirmed by Duncan[17] Huddleson[53] has shown further that this test agrees with the agglutinin absorption test in separating particular strains into abortus or melitensis groups He has described[10] recently a method of separating the bovine porcine and melitensis types through growth sensitiveness toward certain dyes (bacteriostasis) of the triphenylmethane and thiazine series such as methyl violet basic fuchsin and thionin and considers the difference in bacteriostasis toward these dyes presents a rapid and accurate method of determining the type or species of a given strain of Brucella Hardy[54] has confirmed the usefulness of this procedure finding the results definite and in agreement with other tests

Further methods of differentiation of the various Brucella species are found in the metabolic studies of McAlpine and Slanetz[55] They found that Br abortus (bovine) utilizes little or no glucose in its metabolic activities while Br abortus porcine and human used 4–18 per cent of this carbohydrate for growth energy By reason of this difference in sugar metabolism bovine Br abortus can be differentiated sharply from porcine and human Br abortus and Br melitensis by the different amounts of various nitrogen fractions present in the media They further found that an atmospheric concentration of 10 per cent CO stimulates the growth of bovine Br abortus even when accustomed to aerophilic conditions but partially inhibits porcine and human abortus strains and also Br melitensis When CO_2 was entirely excluded all varieties of the abortus melitensis group failed to proliferate The results of their studies show that porcine Br abortus is more closely related to Br melitensis than to the bovine variety Burnet[56] reports a characteristic flocculation of broth cultures of Br paramelitensis at a temperature of 90° C which is peculiar to this species and becomes of diagnostic value His results have been confirmed by Duncan[17]

does not stain by Gram Br abortus tends to be slightly larger than Br melitensis the latter usually being more coccoid in form These differences are inconstant, however, and do not permit a definite distinction to be made between the two varieties Duncan[47] recently has found no marked morphological differences in the various Brucella species on agar or glucose agar, but when it is grown on a relatively rich medium such as Fildes peptic digest blood agar[48], the Br abortus strains frequently develop long bacillary forms, which may reach a length of 2 0–3 0 microns while Br melitensis and Br paramelitensis usually retain the coccoid shape, or rarely exceed a length of 1 0 micron On transferring the cultures back to glucose agar, Br abortus strains again revert to the usual type

Cultural and Biochemical Characters

Primary isolation of the bovine type of Br abortus from pathological material often is difficult The organism usually does not develop at the carbon dioxide tension of air but requires an increased concentration of this gas Huddleson[49] has shown the optimum concentration of carbon dioxide to be 5–10 per cent This peculiar growth requirement distinguishes bovine Br abortus from Br melitensis and porcine Br abortus, both of which grow readily under ordinary atmospheric conditions However after repeated sub-cultures bovine Br abortus usually grows readily in ordinary air In Rhodesia strains of Br abortus isolated from both men and cattle have not shown this dependence upon CO and this fact together with the apparent absence of swine abortion has led Bevan[50] to suggest the presence of a distinct or native variety of Br abortus in that country

Growth of the various Brucella species is extremely slow The optimum temperature is 37° C, and the optimum reaction of the medium is an H ion concentration of pH 6 6–7 4 On agar plates after 36–72 hours incubation, colonies like tiny dew drops appear on the surface of the agar These gradually become opaque as they increase in size during 10–1. days incubation at which time the largest colonies measure about 6 mm in diameter Deep colonies are smaller than those on the surface are more opaque and circular or lemon shaped On agar slants of readily growing strains, there is an opalescent growth after 24 hours which during the next day or two becomes a lustrous moist growth with sharply defined edge Crystals begin to form in the agar after 5–6 days Older cultures become amber or brown with Br melitensis tending toward greater pigmentation sometimes becoming a deep chocolate color Growth at 22° C is very slow and gelatin is not liquified In broth there is a slight initial turbidity followed by a gradual clearing and a finely granular or stringy tenacious sediment Usually no surface ring or pel

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Pathogenicity

Organisms of the Brucella group are pathogenic for a large number of animals In addition to man infection has been demonstrated to occur in monkeys, *goats cattle sheep swine mules, horses dogs* cats, rabbits, guinea pigs, rats, mice chickens and ducks The various species of Brucella are, in general, selective in their hosts Brucella melitensis infecting goats and sheep, bovine and porcine Br abortus cattle and swine respectively, with apparently but little tendency to overlap This does occur however, as Shaw[57] recovered *Br* melitensis from the milk of cows in Malta and Evans[3] produced abortion in a pregnant heifer by injections of Br melitensis with recovery of the same strain from the fetus Evans[3] also reports a human case of undulant fever in Virginia presumably contracted from two cows which recently had aborted Serological tests on the human blood serum and the serum from one of the cows showed infection with Br melitensis A A strain of Br melitensis A was isolated also from a mare in Iowa and another from a cow in Maryland *Burnet has shown* experimentally that Br abortus as well as Br melitensis will produce abortion in goats Schroeder and Cotton were unable to infect cattle by natural methods of exposure to the porcine strain of Br abortus although cows could be infected experimentally and abortion produced They were unable to produce abortion in swine even by injection of bovine abortus[60]

The relative virulence of the different varieties of Brucella still is undetermined, but in general Br melitensis is more *pathogenic for man* and monkeys than the other varieties and the porcine strain of Br abortus more so than the bovine The British Commission[93] fed goat s milk containing varying numbers of melitensis organisms to monkeys with the result that 83 per cent of the animals became infected irrespective of the dosage of bacteria Meyer[61] and his associates were able to infect monkeys with Br abortus provided a sufficiently large dose was used but found Br melitensis far more virulent

Huddleson[67] has found the porcine strain very virulent for monkeys while the bovine infection was mild Human susceptibility to bovine abortus infection undoubtedly is low Burnet[63] was unable to infect men or monkeys by subcutaneous inoculation with Br abortus although controls were infected readily with Br melitensis Otero[64] fed two men cultures of Br abortus (porcine) in milk with the production of undulant fever in both but five men fed similarly with a bovine abortus strain showed no evidence of infection Huddleson[65] recently has examined a group of 500 individuals of all ages approximately equal as to sex, who were exposed *constantly to a milk* supply *infected* with Br abortus and found 1 4 per cent with specific agglutinins in the blood sera and 0 8 per cent actively infected It is agreed generally as shown by Smith[66] and others, that the porcine strain is more virulent than the bovine for

guinea pigs Blumer[67] believes that Br abortus of bovine type is now undergoing an *increase in pathogenicity in view of the great increase in the number* of human infections in the past 3 years Burnet[68] considers Br abortus with its comparatively low virulence for man to be the primitive type of the Brucella group *from* which the *more virulent melitensis and paramelitensis strains* have been derived by modification from passage through the goat Theobald Smith[69] believes that the virulent porcine strain may be a more recent adaptation from the bovine In this connection the following prophecy of Charles Nicolle[70] *is of interest* Mediterranean fever *is in the course of evolution* and is tending to become chronic It is a malady which on account of its manifestations and its chronicity will become one of the commonest and most stubborn diseases Mediterranean fever is a disease of the future

Distribution of Brucella in Nature

Habitat Outside the Animal Body — The organism is an obligatory parasite which is known to multiply only in the bodies of its animal hosts In nature its presence is due to infective discharges from such hosts Its peculiar growth requirements render the isolation of the organism in nature very difficult In Malta repeated tests of dust from infected rooms the air of hospital wards the water of harbors and of soil were uniformly negative

Vitality — Brucella melitensis has been shown to be fairly resistant outside the body retaining its vitality on dried fabrics for 90 days in dry sterilized manured soil for 83 days and in tap water and sea water for 30–4 days In cultures it has been found viable on agar for 76 days in litmus milk for 84 days and in nutrient broth 173 days Eyre[71] found an agar culture incubated at a temperature 18 –22° C viable after 830 days In alkaline urine it will live 6 days and in acid urine for 16 days It is killed in a few hours by direct sunlight Thermal death point with moist heat is 57 5 C for 10 minutes with dry heat 95 C for 10 minutes Phenol in 1 per cent solution and bichloride of mercury 1 000 in watery emulsion will destroy the organism in 15 minutes

Brucella abortus may remain viable in moist manure for 75 days In the placentas of aborting cows exposed under fly screens in shaded places in woods during the colder months of the year it has lived four months[7] Bang and V Stribolt[72] found living organisms in dead mummified fetal membranes nine months after the death of the fetus In discharges from aborting cows it usually dies in less than one month and death is greatly hastened by sunlight In bouillon cultures at room temperature it has remained viable for 8 months and in culture tubes sealed to prevent drying it has remained alive for 3 years Carpenter and Boak[73] found Br abortus artificially inoculated into cream and butter and stored at 8 C remained viable for 10 days in cream and for 142

days in butter The factors most influencing the vitality of the organism appeared to be the percentage of butter fat and the hydrogen ion concentration of skim milk in the cream Artificially inoculated cream failed to infect, when the pH became 5 0, while the higher the percentage of butter fat, the longer the bacteria lived The thermal death point with dry heat at 56° C is about two hours while with moist heat Mohler and Traum[74] killed emulsions in salt solution in 15 minutes at 60° C Carpenter and Boak[7] found that a temperature of 60° C killed the organism in milk in [illegible]o minutes Phenol 5 per cent and bichloride of mercury 1 1000 solution will kill Br abortus in a few minutes

Distribution within the Body

The Brucella melitensis in human beings produces a generalized infection, and the organism has been recovered from the blood, spleen, liver, kidney, urine, adrenal, pancreas, tonsils gall bladder bile intestinal contents, bone marrow, lymph glands thyroid mammary glands milk synovial fluid and pericardial fluid It has not been found in saliva sweat or the cerebro-spinal fluid In acute cases it has been cultured during life from the peripheral blood spleen, urine, synovial fluid and abscess like swellings The organism often persists in the body for long periods appearing irregularly in the blood for months Bassett Smith[76] obtained the organism in pure culture from the spleen during life 18 months after onset of the disease Wainwright[77] reports the recovery of Brucella melitensis in pure culture from an ovarian cyst, six years after the initial symptoms of the infection

Channels of Exit of Brucella Melitensis

In man the principal channel of elimination of Brucella melitensis is through the urine the bacteria making their appearance early in the acute attack Kennedy[78] in a series of 1974 samples of urine examined from 61 cases of Mediterranean fever in Malta recovered Br melitensis in 9 5 per cent of all samples examined The organism was recovered in 54 per cent of patients examined In 43 of the patients the urine was examined repeatedly (over 20 times per case), and in this series the organism was recovered in 72 per cent of the patients In some instances the bacteria were present in enormous numbers but usually were not numerous ranging from 3–4 to 300–400 per c c The excretion of melitensis in the urine tended to occur either as a sudden enormous gush, which stopped as suddenly as it appeared or more commonly as a long continued excretion of small numbers of organisms The bacteria may be present in the urine for months Horrocks[80] found no physical or chemical changes in the urine which were characteristic of the passage of Br melitensis The urine

usually was acid in reaction and free from the opacities and turbidity usually associated with bacteruria An occasional trace of albumin was noted and where mucous deposits occurred these contained greater numbers of organisms

Br melitensis is undoubtedly eliminated in the stools in considerable num bers although due to the cultural difficulties involved their presence has been *difficult to demonstrate* Kennedy[81] *in Malta found the bacteria in the bile in* man and Eyre[82] demonstrated Br melitensis in the gall bladder and throughout *the intestinal tract of artificially inoculated guinea pigs* Eyre[83] *also has demon* strated the organism in the colon of a fatal human case the plate cultures yielding a mixed growth of a large variety of bacteria including Br melitensis By emulsifying some of the growth in salt solution and precipitating Br meli tensis by the addition of a powerful agglutinating serum and again plating he was able to obtain the organism in pure culture Recently Amoss and Poston[84] have added specific serum directly to fecal emulsions prepared from cases of undulant fever with subsequent plating and have isolated Brucella melitensis A and Brucella abortus (porcine) repeatedly in the stools from these cases

Although lactation usually is scanty in women suffering from undulant fever Eyre[85] and his assistants were able to isolate Br melitensis from the milk of two of three cases examined

Modes of Infection and Epidemiology

Sources of Infection

The natural habitat of the various species of Brucella is found in the domestic animals in whom the infection apparently is of world wide distribution. The organism in its various sub species is the principal cause of infectious abortion in these animals and consequently is a source of very serious economic loss Infection occurs naturally in cattle goats sheep swine mules horses dogs cats rabbits guinea pigs rats mice chickens and ducks For man the principal sources of infection are cattle goats sheep and swine The animal source of the infecting organism does not determine definitely its variety as has been shown by Evans[1] and others In general however Brucella abortu (bovine) appears to be the usual infecting organism in the cow Brucella abortus (porcine) in swine and Brucella melitensis in the goat and sheep

1 Brucella Infection in Cattle — Cotton[86] estimates the yearly economic loss in cattle from infectious abortion as equal to or greater than that due to *bovine tuberculosis On account of its economic importance bovine infectious* abortion has attracted more attention and has received more study and investi gation than the disease in other animals although the general characteristics of the infection appear to be similar in all In this country the bovine disease

is of first importance due to its wide prevalence and its relationship to undulant fever in man Animals of any age and sex may contract the disease but pregnant cows are most susceptible The majority of abortions occur in the fifth and sixth months of pregnancy The general health of the animal usually is unaffected The abortions frequently pass unnoticed, and often the presence of the disease in a herd is unsuspected until the scarcity of calves becomes evident Cotton[86] characterizes the infection in the pregnant cow as a disease of neither cow nor fetus but of the structures which lie between the two, the fetal membranes where the organism finds the reduced oxygen content necessary to satisfy its peculiar growth requirements The bovine Brucella abortus exhibits a special predilection for the embryonic tissues of the fetal and maternal placenta also colonizing in the udder of the cow and in the testicles and seminal vesicles of the male and in the corresponding lymph glands It has not been found in other organs (Schroeder) Active multiplication appears to take place only in the fetal membranes of the pregnant uterus with a rapid invasion of the covering epithelium of the embryonic chorion (Smith[87]) and thence spreading between the chorion and the uterine mucous membrane accompanied by the formation of a yellowish or dark brown fibrino purulent exudate

The inflammatory reaction between the fetal and maternal placenta causes a gradual separation of the fetal membranes and interferes with the supply of nourishment and oxygen to the fetus In most cases the result is the expulsion of the fetus and its covering membranes which show the characteristic lesions, thickened indurated membranes and necrotic cotyledons of yellowish gray color The infecting organism can be demonstrated in the stomach contents, liver and gastro hepatic lymph glands of the aborted fetus and is abundant in the resulting vaginal discharge Following abortion Brucella abortus disappears from the uterus usually in two or three weeks but persists in the udder and milk for many years Schroeder[7] states the udder is infected in 60 per cent of infected cows In the udder there are no gross changes but microscopically a mild chronic mastitis can be demonstrated In addition to abortion the infection may cause premature birth retained placenta and sterility Following abortion, the infected cow remains as a chronic carrier of the disease If pregnancy again takes place bacteria again migrate from the udder to the uterus where they may again induce abortion Second abortions however are not frequent and more than two are rare the animals gradually acquiring an immunity which enables them to carry the fetus to term In this manner a herd immunity gradually is established which persists unless non immune animals are introduced into the herd a procedure which is apt to reactivate the infection Abortion, though common is not an absolute criterion of infection as many cows do not abort even though excreting bacteria in their milk

For cattle the most important source of infection is the aborting cow at the

time of abortion and for two or three weeks following The fetal membranes fetus and uterine discharges all contain numerous bacteria The uterine discharges of the infected cow at full term also contain numerous bacteria Such cows act as carriers for many years and are particularly dangerous because unsuspected The most important mode of infection in cattle and the only one proven to infect naturally is by ingestion of food or water soiled with infected discharges Milk from the infected udder is not a common source of infection as the bacteria are few and cows do not usually consume milk

The male does not often convey the infection by the direct sexual act but may carry he disease in his seminal vesicles and infect food and water from genital leakage Calves are relatively resistant to infection during the first five months even when nursing infected cows The organism probably is present in the alvine discharges of calves which are drinking infected milk although this has not been proven definitely Br abortus has seldom been demonstrated in the blood of cattle and for some reason not understood the cow unlike the goat does not appear to excrete the organism in the urine Br abortus is excreted in the milk of infected cows in relatively small numbers usually 0–500 per c c (Carpenter and King[53]) Bacteria are however found frequently in large numbers in the milk of cows near the end of lactation For the detection of carriers of the disease in cattle agglutination tests on the blood serum and milk are employed generally and are of definite diagnostic value Bacteriological examination of the milk may be made by direct cultural methods or by inoculation of guinea pigs the latter method being much more reliable Huddleson[54] has shown that in gravity separation of cream the majority of Brucella organisms are carried up with the rising fat globules and are found in the cream layer

The prevalence of abortion disease in cattle in the United States is wide spread Schroeder and Cotton[56] in 1911 found 14 per cent of 217 samples of market milk positive for Brucella abortus by guinea pig inoculation Fleischner and Meyer[89] in 1917 found that Br abortus was practically always present in the certified milk produced in the San Francisco Bay region and a study by Carpenter and Boak[73] of the milk of 378 cows from three certified dairies showed 6 08 per cent to be excreting Br abortus Carpenter and Baker[90] found Br abortus in the milk of 9 out of 50 herds (18 per cent) supplying the city of Ithaca New York Many states report their cattle heavily infected Connecticut according to McAlpine and Mickle[91] showing 90 per cent of dairy herds infected Carpenter and King[53] estimate that 20–80 per cent of infected cows harbor Br abortus in the mammary glands throughout their lifetime and eliminate it in their milk

2 Brucella Infection in Goats and Sheep — Infectious abortion in the goat must always remain of great interest to the student of undulant fever as this animal was the first proven source of undulant fever of man On June 14

1905, Dr T Zammit[12] of Malta a member of the British Commission on Mediterranean Fever, while carrying out preliminary experiments on goats, found to his surprise, that the serum of five out of six goats not experimentally infected, agglutinated the Micrococcus melitensis (Brucella melitensis) in considerable dilution He was able also to recover the organism from the blood of two of the goats On June 2 1905 Major W H Horrocks[1] a second member of the Commission was able to demonstrate the organism in large numbers in the milk of several of the goats and also in the urine The Commission[12] later came to the conclusion that undulant fever in Malta was due almost entirely to the ingestion of infected goats milk

Goats and sheep are infected mainly through the digestive tract from food contaminated with uterine discharges milk urine and feces of affected animals The infecting organism also may be inoculated during milking into abrasions in the skin Transmission by copulation is also probable as Br melitensis has been demonstrated repeatedly in the vagina from excretion in the urine According to Dubois[n] infection in the goat usually is not manifested by any visible signs the general health of the animal remaining excellent The most important symptom is abortion which occurs in from 50–90 per cent of pregnant goats when the herd is first infected Abortion is most frequent in the fourth month The number of abortions becomes fewer as the herd gradually develops an immunity but a certain number of animals remain infected and act as carriers Fairly often during the course of the disease the animal suffers from sub acute or chronic bronchitis shown chiefly by frequent coughing A mild mastitis is frequent Lameness sometimes occurs from neuritis or arthritis, and orchitis may occur in the male The disease in goats is seldom fatal

The British Mediterranean Fever Commission[1] found that inoculation of goats with Brucella melitensis produced an acute or sub acute septicemia, with the blood and spleen the chief seats of infection in the early stages with later localization of infection in the spleen lymphatic glands and kidneys The infection persisted longest in the lymphatic and mammary glands Brucella melitensis is excreted in large numbers both in the milk and urine Elimination in the urine was inconstant and in 20 goats carefully observed the organism was absent from the urine for a period of two months even when large numbers of bacteria were being excreted in the milk

The diagnosis of infection in the living animal is made through bacteriological examination of blood milk or urine, or the agglutination test in milk (Zammit[93]) and blood Agglutinins may persist in the blood for months. In animals, which apparently have recovered a low grade infection frequently persists, and Zammit[94] states that in his extensive experience he has never known an infected goat to recover completely

The British Mediterranean Fever Commission[1] found 41 per cent of the

goats in Malta infected with Br melitensis and 10 per cent of goats supplying milk were excreting the organism in the milk The numbers of organisms in the milk varied from day to day sometimes being entirely absent and a few days later present in enormous numbers occasionally as many as 3 000 000 per c c In whole milk cheese extensively used in Malta and generally eaten fresh the organism has been shown to survive for 14 days (Bassett Smith[6]) In Texas in 1911 Gentry and Ferenbaugh[9] found that 71 per cent of 151 goats were positive to the agglutination test In a survey of the border counties of Texas Arizona and New Mexico in 1923 Holt and Reynolds[8] found that 16 7 per cent of 1130 goats examined were infected and that some infected herds showed a high percentage of abortions

3 *Brucella Infection in Swine* — In the United States infectious abortion disease in swine has become of increasing importance in recent years especially in Iowa and neighboring states where it is a source of serious loss to the swine industry Infection occurs through ingestion of aborted fetuses fetal membranes uterine discharges and infected milk The disease in swine corresponds very closely to infectious abortion in cattle Like the cow the aborting sow frequently becomes a chronic carrier the infection persisting in the udder for months or years

4 *Brucella Infection in Man* — While the undulant fever patient does not appear to be an important source of human infection he should justly be considered a potential source of disease The organism usually is present in the urine often in enormous numbers Kennedy[78] finding them in 72 per cent of patients in whom repeated and careful search was made Recently by a refinement of technique Amoss and Poston[31] have isolated Br melitensis and Br abortus (porcine) from the stools of infected persons Shaw[97] has shown that in Malta the human ambulant carrier is to be reckoned with In examining the blood of 525 dock laborers he found 79 (15 per cent) positive to the agglutination test From several of the positive cases he isolated Br melitensis from the blood and urine and proved such cases to be excreting large numbers of virulent organisms in the urine over long periods

Routes of Infection

1 *The Gastro intestinal Tract* — It has been established definitely that the great majority of cases of undulant fever contract the disease through the ingestion of infected milk Milk products such as ice cream cheese and butter which are made from unpasteurized infected milk also may convey the disease The organism is able to invade the normal mucous membrane of the gastro intestinal tract and then gains entrance to the circulation The British Commission on Mediterranean Fever came to the conclusion that undulant

fever in the military and naval forces stationed at Malta was almost entirely due to the ingestion of infected goats' milk, and the elimination of raw goats' milk as an article of diet promptly resulted in an almost complete disappearance of the disease. The Commission found Br. melitensis in goats' milk extremely virulent for monkeys, 83 per cent of experimental animals contracting the disease irrespective of the dosage of the organism[98]. That Br. melitensis in goats' milk is similarly virulent for man was demonstrated in the famous case of the steamship "Joshua Nicholson,"[99] where members of the crew freely used the milk of a herd of goats which was in transit from Malta to the United States via Antwerp. Of twelve individuals whose history could be verified, it was found that eight contracted undulant fever. Of the remaining four, two had boiled the milk always and two had used very little as it disagreed with them. Examination of the goat herd on arrival in the United States showed several goats to be excreting Br. melitensis in their milk, and eventually all of the goats had to be destroyed. In an epidemic of undulant fever at Phoenix, Arizona, in 192 Lake[100] found that of thirty cases, all but three had drunk goats' milk from the same dairy, and in these the same source of infection could not be excluded.

The ingestion of raw cows' milk or milk products is the usual source of undulant fever in the United States. Carpenter and King[55] in reviewing 155 cases of undulant fever in the United States definitely diagnosed as due to Br. abortus found 109 (70.3 per cent) gave a history of drinking raw milk, which in the majority of cases was proven to be infected with Br. abortus. These authors further report that serum examinations of 530 individuals known to have drunk raw milk containing living Br. abortus from a single herd in which 54.6 per cent of the animals were infected showed that 13 per cent contained specific agglutinins for Br. abortus, 8 individuals were ill of undulant fever at the time of examination and others gave a history suggestive of the disease. In contrast, the blood sera of 690 individuals known to have drunk raw milk free from abortus infection or pasteurized milk showed no agglutinins nor did any cases of undulant fever develop in this group. Huddleson[101] in Michigan reported a series of 31 cases of undulant fever all using raw cows' milk regularly. In 23 cases information as to the milk supply was obtained and definite evidence of Br. abortus infection in the cattle supplying of the patients was found. He concluded that in Michigan the consumption of raw milk from cattle infected with infectious abortion is primarily responsible for the undulant fever infection in man. The widespread presence of Br. abortus in cows' milk with the low incidence of disease in man indicates that Br. abortus is only slightly pathogenic for man and it would appear that only the more virulent strains are capable of producing disease.

2. *Skin and Mucous Membranes.* — Cutaneous inoculation is a not infrequent

mode of infection The British Commission found that the disease could be transmitted readily to goats by rubbing infected milk upon the shaven udder[10?] and considered that the frequent presence of undulant fever in the families of goat owners (who do not as a rule use the milk) was due to cutaneous inoculation through scratches and abrasions of the human skin[103] Gentry and Ferenbaugh[9?] in 1911 found that the greatest incidence of undulant fever among the goat ranchers of Texas occurred in the months of March to June inclusive during which period the whole family practically lives with the goat herds caring for the kids and teaching them to suckle De Korte[104] in 19 4 reported a case of undulant fever in South Africa in which the patient had contracted the infection apparently through manual removal of the placenta from a cow suffering from infectious abortion Hardy[10] recently has called attention to the frequency of undulant fever in Iowa among farmers and packing house workers and considers that cutaneous inoculation from animal discharges or tissues is not uncommon Infection occurred in 58 farmers but in only 8 farmers wives a relative proportion which clearly indicates a source of infection other than milk He also cites the case of a packing house worker who developed undulant fever 17 days after injuring himself while cutting hogs He[?] has found the unabraded skin of the guinea pig a more ready portal of entry than the digestive tract A French commission consisting of Aublant Dubois Lafenetre and Lisbonne[10?] reported in 19 6 that direct contagion was nearly as important as the ingestion of infected food

The organism has been shown to be transmitted readily through the unbroken mucous membrane Shaw[107] infected monkeys by instilling an emulsion of Br melitensis into the conjunctival sac and Schroeder and Cotton were able to infect a heifer by permitting a single drop of Br abortus culture to fall into the eye The British Commission[107] was able to infect monkeys through the unbroken mucous membrane of the glans penis In view of the demonstrated existence of Br melitensis in the urine and vaginal swabbings of infected women they pointed out the possibility of infection of man during sexual congress

3 Respiratory System — The organism is able to retain its vitality for several months in a dried condition and the British Commission[109] was able to produce the disease in monkeys through the inhalation of infected dust The majority of experiments were negative however and it is evident that this cannot be a frequent source of infection

Incidence and Distribution in the United States

Craig[110] in 1905 reported the first case of undulant fever originating in the United States The patient was a nurse in a Washington, D C hospital The source of infection was not determined but apparently it was not contracted

from goats At that time, Craig predicted that many of the obscure continued fevers of the United States would prove to be undulant fever No further cases were reported until 1911 when Ferenbaugh[111] and Gentry and Ferenbaugh[96] reported the presence of endemic Malta (undulant) fever in southwestern Texas and concluded that the disease had been present in that locality for at least twenty five years All cases reported were associated with the goat raising industry and 19 4 per cent of 128 goats examined gave a positive agglutination test Several sporadic cases were reported in southwestern United States during the succeeding decade all considered to be derived from goats In 1922 Lake[100] and Watkins and Lake[11] reported an epidemic of 37 cases in Phoenix, Arizona

The discovery by Evans in 1918 that the organism causing undulant fever was closely related to that causing infectious abortion of cattle, and the report of Keefer in 1924 of a proven case of undulant fever due to Br abortus served to arouse widespread interest in the disease throughout the United States Serological tests on fevers of unexplained origin have shown that the disease exists in all sections of the country Hardy[113] in Iowa performed a comparative series of agglutination tests for typhoid paratyphoid and undulant fever on 1120 sera received at the State Laboratory between Dec 1 1927 and June 30, 1928 finding 50 sera positive for typhoid and paratyphoid on 47 patients and 1 6 sera positive for undulant fever on 74 patients He considered that the tests showed that undulant fever is at least as prevalent in Iowa as typhoid and paratyphoid fevers combined Carpenter and Chapman[93] in New York tested 4050 sera sent in to the Bureau of Health Laboratory for routine Wassermann tests and found Br abortus agglutinins in 7 3 per cent Giordano and Ableson[114] examined 1100 sera in Indiana and found 63 (5 7 per cent) positive for Br abortus The large number of cases reported in limited areas where

TABLE I UNDULANT FEVER BY STATES

Alabama	4	Maine	13	Ohio	111
Arizona	69	Maryland	23	Oklahoma	2
Arkansas	1	Massachusetts	2	Oregon	1
California	51	Michigan	88	Pennsylvania	29
Colorado	1	Minnesota	42	Rhode Island	1
Connecticut	23	Mississippi	2	South Carolina	22
Delaware	4	Missouri	31	South Dakota	4
Dist of Columbia	6	Montana	3	Tennessee	118
Florida	2	Nebraska	6	Texas	43
Georgia	37	Nevada	2	Utah	3
Idaho	2	New Hampshire	0	Vermont	3
Illinois	48	New Jersey	11	Virginia	9
Indiana	56	New Mexico	18	Washington	3
Iowa	230	New York	145	West Virginia	0
Kansas	24	North Carolina	5	Wisconsin	28
Kentucky	49	North Dakota	7	Wyoming	0
Louisiana	2				

careful investigations have been made indicates that most of the cases are at present unrecognized and the true incidence of the disease therefore cannot be stated accurately at this time That an improvement in diagnosis of the infection is now taking place is evidenced by the fact that in the year January 1 19 9–December 31 1929 inclusive 964 cases of undulant fever were recognized in the United States[115] Hardy[116] has collected reports of 1430 cases in continental United States prior to June 1929 distributed as noted in Table I

The cases in Texas Arizona and New Mexico are associated closely with the goat raising industry Elsewhere in the United States cattle appear to be the principal source of infection, with a center in Iowa and several surrounding states where swine are also an important source of infection

Seasonal Prevalence

In Malta it was noted by Hughes[117] and others that the admission rate was lowest in the first quarter of the year rose rapidly in May remained high in the hot dry months of July August and September and then subsequently declined to a low rate in December January and February With the discovery that the goat acted as the carrier of the disease this seasonal prevalence was readily explained The kidding period occurs in the spring with freshening of the milch goats and thus during the summer a large amount of infected goats milk was available coincident with an increased demand for liquid refreshments

In Texas Gentry and Ferenbaugh[96] found the majority of cases of undulant fever in goat ranchers occurred from March to July a period which embraces the kidding season in the goats and the time when the goats are in full milk During this period the whole family were in direct contact with the goat herds caring for the kids and teaching them to suckle

No accurate statistics are available at present as to seasonal incidence of undulant fever due to Br abortus It will doubtless be found however that the warm months during which time the consumption of milk and milk products is increased greatly will prove to be the period of greatest incidence

Place of Residence

Undulant fever is largely a disease of rural districts and small towns Hardy[118], in an analysis of 125 cases occurring in Iowa found 65 patients living on farms 11 in towns of less than 1000 population 21 in towns of from 1000–5000 population 2 in cities of 5000–10 000 population 23 in eight cities of more than 10 000 population and 3 became ill while travelling Twelve of the 23 urban cases occurred among packing house workers In Denmark Madsen[119] in 209 cases found 145 living in rural districts and 64 in towns or cities

Age

The majority of cases of undulant fever occur in young adults. Hardy[54] in the United States in 713 cases found that 459 or 64.4 per cent occurred between the ages 20-45. Evans[9] reports similar findings. Madsen[119] in Denmark found men from 15-40 provided the majority of cases (56.4 per cent) and found no characteristic age grouping for females. In 134 cases, having direct contact with live stock or animal carcasses Hardy[54] found 99, or 73.8 per cent, in the age group 20-45 which in general follows the curve of age grouping for males. The age grouping of females parallels the age distribution of cases not associated with live stock or carcasses. Hardy considers that the age distribution is dependent on two factors: a variation in susceptibility and a variation in direct exposure to infected animals.

Most observers note the rarity of cases in children. Hardy[54] in the United States in 713 cases found only 4 cases under 4 years of age and a total of only 20 cases under 10 years of age. Madsen[119] in Denmark found no cases in children under 8 and states that undulant fever has never been observed in the hospitals or asylums for children in Copenhagen, where raw milk is used in large quantities. Larsen and Sedgwick[110] however examined the sera of 425 children by complement fixation test and found 17 per cent showed antibodies for Br. abortus while 42 children[111] who had never used cows' milk, were negative. The scarcity of the disease in children is hard to explain, as children habitually use more milk than adults. Hardy believes that during the early years of life an immunity may be acquired without apparent disease or through a mild infection the cause of which is not recognized and hence it is not diagnosed as undulant fever.

Sex

Males greatly predominate in total reported cases. Hardy[54] in 877 cases in the United States found 614 or 70 per cent males. Madsen[119] in Denmark in 222 cases reported 166 or 75 per cent males. Hardy[54] found however, that in 75 cases having no direct contact with live stock or carcasses only 37 or 49 per cent were males and 38 or 51 per cent females, while in 147 cases in families having direct contact with animals 136 or 93 per cent were males and 11 or 7 per cent females. Further of the 11 females 6 gave a history of repeated and direct contact with live stock. It is generally agreed that males are not more susceptible than females when equally exposed to infection and that the greater proportion of males is dependent on contact exposure incident to the difference in type of occupation of the two sexes.

Occupation

Hardy[113] in an analysis of 125 cases in Iowa found that 8 were engaged in occupations which gave more or less direct contact with live stock meats, or dairy products Among these were 56 farmers 8 farmers wives 3 stock buyers 12 packing house workers 2 workers in dairy products plants and 1 butcher In Michigan Huddleson[101] found more cases in farmers than in any other occupation Gentry and Ferenbaugh[95] in Texas found the majority of cases of undulant fever to occur in goat ranchers and their families Hardy[113] calls attention to the frequency of infection in workers in packing houses and states that for workmen s compensation purposes undulant fever in packing house operatives must be considered as an occupational disease Bacteriologists and laboratory workers are especially liable to infection with Br melitensis and many of the prominent students of undulant fever have contracted the disease

Immunity

Bruce[122] considered that one attack of undulant fever conferred immunity against subsequent attacks Hughes[117] found that while one attack of the disease appeared to give an immunity for a number of years that this immunity was by no means absolute He cites the case of an officer who had two definite infections with an interval of twenty four years between attacks He also found it impossible to lay down a period after which the convalescent patient became proof against relapse This observer further noted a certain degree of protective immunity in the adult civilian population of Malta which he ascribed to infection in youth Shaw[123] observed that monkeys which had recovered from an experimental infection reacted less markedly than others to the same dose of living organisms and considered that the previous attack conferred some degree of immunity Bassett Smith[76] from his extensive experience with undulant fever finds that immunity following the disease is only slight and that secondary infections do occur

Although infection with organisms of the Brucella group usually is followed by the production of specific agglutinins in the blood serum Durham[39] and also Eyre[124] have shown that there is apparently little direct relationship between agglutinins and antitoxic or antibacterial substances The blood of infected animals frequently showed a high agglutinating power for some time prior to a fatal termination Eyre[124] further has shown that repeated injections of killed cultures of Br melitensis in rabbits with the production of a high agglutination titer in the blood did not protect against fatal infection when the animal wa subsequently inoculated with comparatively small amounts of a virulent cul

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acute and chronic endocarditis involving the mitral and aortic valves associated with Br melitensis (variety abortus) bacteremia The patient gave a previous history of rheumatic fever however and the Brucella infection was not proven as the etiologic factor Eyre[52] noted an increased permeability of the walls of the blood vessels evidenced by ready bruising from trivial causes during life and at autopsy by localized extravasation of blood in the sub peritoneal connective tissues He considered the condition to be the result of action of the specific bacterial toxins on the vasomotor system

Respiratory System — The lungs usually show hypostatic congestion and edema at the bases associated frequently with lobular pneumonia In 15 cases where the condition of the lungs was clearly noted Hughes[117] records marked congestion with lobular consolidation of the bases of both lungs in 11 a similar condition in left lung with congestion only in right lung in one case and in three cases congestion without consolidation Pleurisy is not uncommon although the specific organism has not been isolated from the pleuritic fluid

Gastro intestinal System — Small areas of congestion usually are found distributed throughout the intestinal canal associated with edematous swelling and softening of the mucous membranes It is important to note that ulceration of Peyer s patches seldom occurs In chronic cases superficial ulceration of the mucous membrane is found occasionally usually occurring in the colon

Mesenteric Glands — These frequently are enlarged Kennedy[81] reports a case where the enlarged glands were filled with fluid pus containing a pure culture of melitensis organisms

Liver — This organ usually is congested somewhat enlarged and increased in weight Microscopically there is cloudy swelling of the liver cells with small round cell infiltration in the interlobular tissues The infecting organism is found in large numbers in the liver and to a less extent in the gall bladder Eyre and Fawcett[1 ?] report a fatal case of sub-diaphragmatic and hepatic abscess which is of interest because Br melitensis rarely causes suppuration

Spleen — Hypertrophy invariably is present Hughes[117] in 6 acute cases found the spleen varied in weight from 10–24 ounces the average being 19 9 ounces or about three times the normal size The organ was extremely congested dark red to black in color and usually soft and friable Microscopically there was intense congestion with great distention of the sinuses with blood and a marked increase in the lymphoid cells of the Malpighian bodies Bassett Smith[78] reports a chronic case dying in 18 months whose spleen weighed 56 ounces Small hemorrhages or infarcts may be present The spleen contains large numbers of specific organisms

Genito urinary System — The kidneys sometimes are congested but frequently no abnormality is noted Occasionally large pale kidneys are found resembling the large white kidney of chronic Bright s disease Cloudy swelling

ture Immunization of soldiers in Malta by prophylactic inoculation with Br melitensis vaccine was attempted on a small scale by the British Commission, but the results were inconclusive Immunization of domestic animals with killed and living cultures especially the latter has produced a certain degree of immunity, but the procedure has not been of great value in eradicating the disease

As noted above young children appear to be relatively immune to infection, or, if infected may acquire an immunity without evident disease Cotton[86] states that calves up to the age of three months and possibly six months, are immune to infection although specific agglutinins may be present in the blood The Mediterranean Fever Commission[1] found that an appreciable amount of specific agglutinin was transferred from infected goats to their offspring in utero and that young kids appeared to be immune to infection even when nursing dams whose milk was loaded heavily with Br melitensis This immunity proved to be relative however and was overcome easily by inoculation with living cultures

Pathology

Our knowledge of the pathology of undulant fever in man is limited Due to the low mortality of the disease opportunity for thorough study of autopsy material is lacking and such information as we possess is derived largely from the observations of medical officers of the British Army and Navy in Malta Br melitensis produces a generalized infection in man as previously described Post mortem evidences of the disease are few not characteristic, and are the result of the direct action of the infecting organism or its toxic products, upon the tissues The findings are dependent largely upon the stage of the disease in which death occurs Hughes[117] who collected data on 62 post mortem examinations in Malta noted in the acute and rapidly fatal cases, signs of intense congestion especially marked in the internal organs In the chronic cases, he found death generally to be the result of heart failure broncho-pneumonia or other secondary infection or sudden febrile exacerbation In addition to the signs of local and immediate cause of death the tissue showed a chronic irritation similar to that seen in chronic poisoning The morbid anatomy of undulant fever may be summarized as follows

Cardiovascular System — The heart usually is normal in appearance The pericardial fluid frequently is increased in amount and usually contains the infecting organism Occasionally definite pericardial effusion is present Hughes[117] in 62 autopsies noted a vegetative endocarditis in five cases four involving the mitral and one the aortic valve Two of these cases, however, he considered to be of previous origin Scott and Saphir[128] report a fatal case of

which may last from a few weeks to several years and in which every gradation in severity may occur from scarcely recognizable indisposition to a state of overwhelming toxemia Hughes[117] who observed over 1000 cases in the hospitals of Malta and whose clinical description of the disease remains unrivalled states So variable are the symptoms and so uncertain is the duration and course of this fever that it is impossible to give a description to which all cases can be referred The most constant clinical features of the disease may be said to be indefinite duration irregular course and low mortality Although no definite clinical distinction can be made between infections with the various species of Brucella it would appear that Brucella abortus produces in general, a milder form of the disease than does Brucella melitensis

Clinical Types

Hughes[117] from a careful study of the pyrexial curves of his large series of cases differentiated three main types of the disease malignant undulatory and intermittent although irregular and mixed types also were seen frequently To the classification of Hughes Bassett Smith[76] would add two additional types ambulatory and mild forms Eyre[91] differentiated three types acute subacute and chronic according to the severity of the dis ase although he recognized these distinctions to be purely arbitrary

1 *Ambulant Form* — Th s cases were recognized first by Shaw[97] Symptoms may be entirely absent or are limited to a fe v days of slight fever These cases are unrecognized unless sought for by examination of the blood for specific agglutinins or for the presence of the organism These patients may however excrete virulent organisms in the urine in large numbers over long periods of time and are potential sources of infection

Mild Form — These are frequent and often unrecognized or may be confused with malaria or paratyphoid fever There may be a feeling of lassitude headache constipation indigestion thirst and slight sweating with a slight irregular fever lasting from a few days to two weeks The temperature rarely rises above 102 F falling one or two degrees in the morning and is usually of an irregular remittent character With the return of the temperature to normal convalescence rapidly follows

Undulatory Form — This is the most common form especially in Brucella melitensis infections Hughes[117] has well described its characteristic febrile course as marked by intermittent waves or undulations of more or less remittent pyrexia of variable length separated from one another by periods of temporary abatement or absence of symptoms This repeated alternation of waves of pyrexia with periods of normal or nearly normal temperature has given to the disease its name of undulant fever The onset usually is insidious

is seen often in microscopical sections and the Brucella organisms are present frequently The specific organism appears to have a special predilection for the generative organs orchitis epididymitis and prostatitis being not infrequently noted in the male and mastitis and ovaritis in the female

Bones and Joints — The bone marrow was found by Eyre[83] to be normal in gross appearance but microscopically there was a marked increase in nucleated red cells and lymphoid cells with considerable diminution in the granular cells Brucella organisms often are present and Burnet[15] considers that the Br melitensis finds a resting place in the bone marrow when absent from the blood

Arthritis is common but usually disappears in a few days without apparent damage to the joint Kennedy[12] however has seen a number of cases of purulent synovitis of the costochondral joints

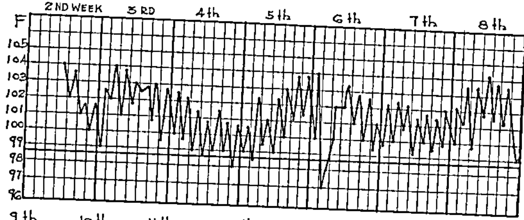
Nervous System — Hughes[117] found congestion of the meninges, superficial veins and choroid plexus usually present with some increase in cerebrospinal fluid Kennedy[91] noted flattening of the cortical convolutions when the cerebrospinal fluid was increased Eyre[83] states that the brain and spinal fluid usually appear normal The specific organism has not been isolated from the cerebrospinal fluid De Nunno[130] has found that the melitensis toxin causes degenerative changes in the nerve cells with breaking up of the nerve fibrils and leucocytic infiltration most marked in the cerebrum and medulla The peripheral nerves also were severely involved, which he considered to explain the frequency of peripheral neuritis

Incubation Period

This has given rise to much discussion as the onset is very gradual in the naturally acquired disease Bruce states that cases have occurred in 6 days after arrival at Malta but considered the usual period to be 14–17 days Hughes[117] believed that the incubation period might be as short as 3 days but that 10–15 days was the rule Bassett Smith[6] considers the incubation period varies from 6 to 20 days Johnstone[131] from his epidemiological studies considered 14 days the usual period He cites a number of accidental laboratory infections as conjunctival inoculation 5 days drawing living cultures into mouth 6 and 8 days and subcutaneous inoculation 15 days Infection by inoculation is usually shorter than by feeding Shaw[17] in subcutaneous inoculation of monkeys, produced infection in periods varying from 2 to 7 days

Symptomatology

The clinical manifestations of undulant fever are extremely variable Diversity of symptoms is to be expected in the course of a generalized infection,



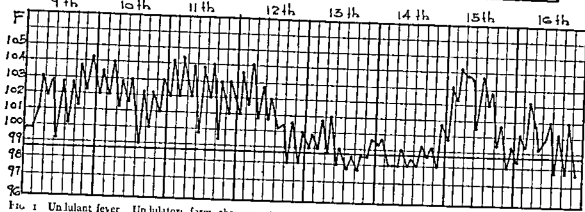


Fig. 1. Undulant fever. Undulatory form showing intermittent waves of remittent pyrexia. Brucella melitensis variety melitensis infection. (After Watkins and Lake.)

For some days there is an ill defined feeling of malaise with lassitude, anorexia, slight headache thirst and constipation The individual is depressed, there is increasing nervous irritability and insomnia Muscular pains, described as rheumatic ' often are felt in back, neck and limbs, and a slight evening rise of temperature occurs associated with chills Less frequently, the onset is more abrupt with acute fever, gastric irritability and sore throat As a rule however the temperature rises gradually, remitting each morning about half the amount of the rise of the previous evening until an elevation of 103°-105° F is reached The step like character of the ascent resembles that of typhoid but the prostration apathy and toxemia of typhoid are wanting Indeed in the early stages of undulant fever the patient often exhibits a singular lack of discomfort which is most unusual in view of the height of the pyrexia He endeavors for a time to carry on his usual occupation, but eventually is forced to desist The headache usually frontal, increases the tongue is coated, moist swollen and indented laterally the breath is offensive there is apt to be epigastric or perisplenic tenderness and the bowels become markedly constipated There is often bronchitis or hypostatic congestion of the lungs in proportion to the severity of the case Each remission of temperature almost invariably is followed by profuse sweating There is increasing debility and restlessness and insomnia become more marked After a variable period lasting from ten days to three weeks there is a gradual decline of temperature corresponding to the ascent until normal or nearly normal levels are reached With the decline of the fever there is marked amelioration of all symptoms and the primary wave of pyrexia is now over The patient may wish to get up, but if he does so a severe relapse promptly follows After a few days of approximately normal temperature the characteristic pyrexia returns and a relapse similar to the primary attack occurs although usually less prolonged and less severe This in turn subsides to be followed later by other relapses so characteristic of this fever which are variable in number and duration

With the progress of the disease the liver and spleen become tender and enlarged there is increasing anemia and progressive loss of weight Obstinate constipation is the rule although in severe cases there may be diarrhea The drenching sweats usually nocturnal continue and may be very distressing Symptoms of neuritis may appear now with chronic sciatica or intercostal neuralgia as the most frequent manifestations although practically any nerve may be affected Painful hyperesthesia of the feet which is aggravated by pressure of the bed clothes is not uncommon An acute transient arthritis involving one or more joints often occurs the affected joint being hot, swollen and extremely tender the process rapidly subsiding in a few days in one joint only to recur in others Involvement of the sacro iliac joints is especially painful An acute orchitis is not infrequent With the repeated relapses, the pa

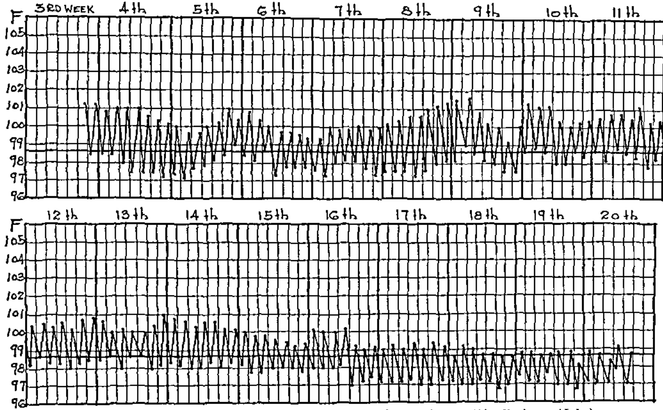


Fig 3 Undulant fever Intermittent form Brucella melitensis variety melitensis infection. (After Watkins and Lake)

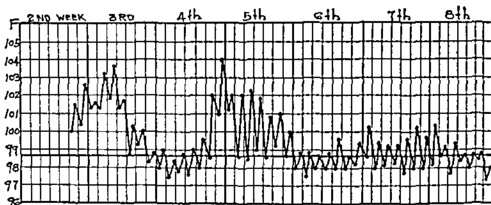


Fig 2 Undulant fever Mild undulatory form Brucella melitensis variety abortus infection

tient becomes more and more emaciated anemic, debilitated and despondent He is subject to attacks of bronchitis or even at times to bronchopneumonia The pulse rate becomes increased and cardiac palpitation occurs on slight exertion Rheumatic or neuralgic pains are common The temperature now tends to become intermittent and this feature, with the cough, emaciation and profuse night sweats is very suggestive of phthisis Toward the end of the third month the temperature becomes normal in the morning with only a slight evening pyrexia This is followed by a period of subnormal temperature and improvement in all symptoms and convalescence is now established Complete recovery is slow however, and for a number of months he is liable to attacks of neuralgic pains arthritis or orchitis with the return of slight pyrexia The duration of pyrexia in the average case is about 60 days, the usual length of each pyrexial wave being about 10 days The period of invalidism from the disease averages 3 or 4 months but *may persist for* ? or more years

4 *Intermittent Form* —The onset is more gradual the general course of the disease is milder than in the undulatory type and relapses are less frequent At the onset, there is a sense of weakness and lassitude with slight evening headache The appetite is diminished the tongue is coated and the individual notices a bad taste in the mouth on waking in the morning The temperature is normal or subnormal in the morning rises to about 99° F in the afternoon and returns to normal during the night The headache becomes more noticeable general muscular pains occur and there is restlessness insomnia and nocturnal sweating Constipation is a noticeable feature The pyrexial curve now assumes its characteristic form The temperature is normal or nearly so in the morning rises slowly to a maximum of 99 –105° F between 2–5 P M often associated with chilliness and falls gradually to normal during the night, the pyrexial fall being accompanied by profuse sweating This hectic type of tem

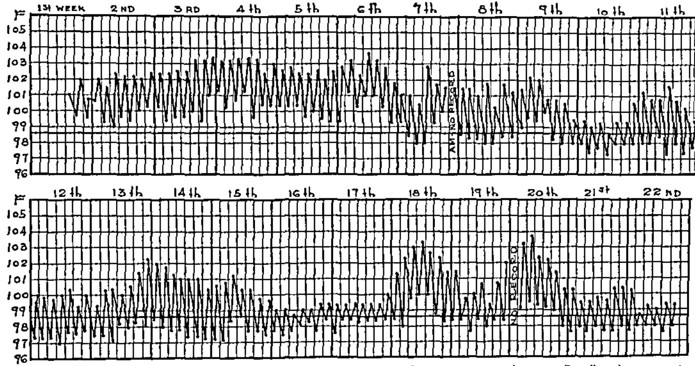


Fig 4 Undulant fever Unusually long case showing undulatory remittent and intermittent type of pyrexia Brucella melitensis variety abortus infection (Courtesy of H I Hasseltine Surgeon U S Public Health Service)

perature may persist for days without serious complications, and, except during the afternoon when the fever is high, the patient eats well and has few complaints

Fleeting joint pains, neuritis and orchitis may occur in the later stages of the illness The pyrexial period seldom is prolonged beyond 6 weeks, but the disease may persist for six months or more Hardy[118] and also Simpson and Frazier[133] consider the intermittent type to be the most common one in infections with Br abortus in the United States In the experience of these observers the average duration of the disease is three or four months

5 *Malignant Form* —This type as described by Hughes[117], is responsible for most of the deaths in undulant fever but fortunately is rare The onset usually is sudden with severe headache pains throughout the body and marked gastric symptoms The temperature on admission may be 104°–105° F Abdominal tenderness is present and the breath and skin odors are very offensive After several days of continuously high temperature pulmonary congestion and bronchopneumonia may appear Diarrhea with frequent and very offensive stools may be present The temperature may decline slightly but usually remains around 103° F Cardiac irregularity increasing pulmonary congestion and obstinate vomiting occur followed by delirium which soon passes into coma The patient becomes incontinent the temperature rises steadily, the heart fails and the patient dies from hyperpyrexia and toxemia In 45 fatal cases cited by Hughes, 27, or 60 per cent, died within the first month of the disease

Special Clinical Features and Complications

Appearance —A striking feature in many cases especially in the early weeks of the disease, is the comfortable appearance of the patient Even though a high degree of pyrexia may exist he usually is mentally alert and ready to talk This is in marked contrast to the apathy dull appearance and prostration seen so frequently in typhoid fever In the severe cases with high temperature the face usually is flushed and the conjunctiva injected Chronic cases often present an air of listless resignation and where marked emaciation and anemia have occurred may resemble phthisis

Fever —This is the most important and at times the only clinical finding According to Hughes, the chief characteristics of the fever are the variation in amount and duration of pyrexia in different cases and the tendency to form a series of intermittent waves or undulations of remittent pyrexia The types of pyrexia have been described previously Eyre[93] in an analysis of 1000 temperature curves in Br melitensis infection found 58 per cent remittent, 26 per cent continuous, 14 per cent intermittent and hyperpyrexia in 2 per cent

often were diagnosed ' Mediterranean phthisis which was found to recover remarkably when given a change of climate A fibrinous pleurisy occasionally may occur

Digestive System — The tongue from the onset, usually is swollen thickly covered on the dorsum with whitish yellow fur and indented laterally by the teeth In severe cases it becomes dry and deeply fissured with patches of the surface denuded of epithelium The condition of the tongue serves as a reliable index of the severity of the disease and a normal temperature seldom is established until the tongue becomes clean The fauces are congested, and the breath is offensive Appetite and digestion are impaired in proportion to the severity of the illness although in protracted cases the patient s appetite is apt to be greater than his powers of digestion Constipation often obstinate is a characteristic feature of the disease occurring according to Hughes, in 81 per cent of cases Diarrhea however may be present in severe cases The stools usually are offensive Epigastric tenderness often is seen especially over the enlarged spleen and the liver frequently is enlarged and tender A rare complication is hepatic and subdiaphragmatic abscess, which occurred in a fatal case reported by Eyre and Fawcett[17]

Lymphatic System — The spleen usually is moderately enlarged and is tender in the early stages The organ is palpable in over half of the cases usually only on inspiration although sometimes it extends downward almost to the navel The lymph glands of the neck and groin may be enlarged but do not suppurate

Cardiovascular System — The pulse in the early stages of the disease is slow and firm but later, especially in severe cases the rate is rapid and often intermittent Cardiac palpitation occurs on slight exertion or emotional stress This probably is due to the effect of the specific toxin on the vasomotor system but the heart muscle also may be directly affected In severe cases death usually is due to heart failure Organic heart disease is extremely rare Hughes[117] observed valvular changes in but four cases, where it was not known to be present previously Pericardial effusion is rare but is of serious import Hughes[117] records two cases both of which were fatal Epistaxis is very common in the later stages of the disease Phlebitis may occur rarely

Blood — A moderate anemia of secondary type is commonly present in protracted cases The red cells usually vary from 3–4 million per cu mm with a corresponding reduction in hemoglobin While a leucocytosis has been reported occasionally in early acute cases as a rule the white cells are normal or slightly below normal The lymphocytes are relatively increased usually numbering 40–50 per cent

Nervous System — The specific organism and its toxins appear to have a selective action on the nervous system, and the nervous manifestations are

Hughes[117] found the average length of 300 febrile waves to be about 10 days, the primary wave being longer, 18–3 days The number of waves in an attack varied from 1–7 (average 3) and the interval between waves was 1–10 days (average 3 or 4 days) The pyrexial duration is very indefinite and may vary from a few days to several years Hughes found the average pyrexial duration in 372 cases to be 58 days

Hyperpyrexia although rare is a serious and often fatal complication It may appear at any time during the course of the disease but usually follows a continuously high temperature either early in malignant cases or during a severe relapse The temperature rises steadily to 106°–108° F shortly before death

Skin and Appendages —Skin eruptions are seldom found in undulant fever, although sudamina are not uncommon after the sweating becomes profuse. Furunculosis occurs frequently in debilitated patients Hughes[117] noted small temporary subcutaneous nodules occasionally on the face and extremities. Giordano and Ableson[114] noted in two cases a macular rash on the face, extremities and chest associated with intense itching and Craig[110] reported a case in which a maculopapular rash appeared and disappeared several times during the course of the fever Subcutaneous hemorrhages of a purpuric character have been noted occasionally in severe acute cases Desquamation is common, usually occurring about the fourth week most noticeable on the soles of the feet. With the development of anemia the skin shows a marked pallor and often bronzing while the tissues around the eyes and over the ankles may become edematous A distinctive and disagreeable odor described by Hughes as goat like is given off from the skin and breath in nearly all cases and may be very offensive in severe cases Following a severe attack the hair often becomes gray, and the patient seems to age rapidly In chronic cases the hair frequently falls out extensively being gradually renewed during convalescence The nails in protracted cases often are transversely grooved or longitudinally striated

The sweats are characteristic of the disease Each remission of fever is almost invariably followed by profuse perspirations which may be very debilitating and depressing They tend to increase in severity with the progress of the disease The time of sweating is dependent upon the pyrexial curve, but usually occurs from eleven P M to three A M The night clothing often is drenched and requires frequent changing Although usually general sweating may be localized to certain portions of the body as the face or one arm

Respiratory System —Some degree of bronchitis with a sticky mucous expectoration usually is present and Hughes[117] found evidence of basal congestion in 95 per cent of protracted cases In severe and malignant cases, bronchopneumonia may occur and is a serious complication In former years patients with bronchitis, hectic temperature copious night sweats and emaciation

cations occurring in from 4–8 per cent of cases as a late manifestation The condition usually is mild subsides in a few days, and there is no apparent tendency to testicular atrophy or to sterility Simpson and Frazier[135] report the isolation of Br abortus from a draining sinus tract which extended from the globus major of the epididymis through the scrotal wall Due to the increased nervous irritability sexual desire may be increased and priapism is common

In women mastitis often occurs with scanty lactation and the specific organism may be present in the milk The menstrual functions usually are undisturbed although amenorrhea may occur in severe cases with marked anemia Wainwright[77] reports the removal by operation of a cystic ovary containing a pure culture of Br melitensis six years after onset of the disease

Pregnancy — Abortion may occur in the pregnant woman following infection with organisms of the Brucella species but this complication would appear to be less common in human beings than in the lower animals In Malta Hughes and also Fyre observed no effect upon the ordinary course of pregnancy from infection with Br melitensis Samut[136], in Malta however reported abortion of a five months still born fetus about three weeks after onset of infection in the mother Levi[137] in Tunis reported that of 11 pregnant women having undulant fever, abortion occurred in 6 De Forest[138] reported a series of 11 cases of abortions and still births in women in whom the clinical course of the disease and intra uterine pathology corresponded to that of cattle infected with Br abortus None of these cases however, were confirmed by serological or bacteriological tests Simpson and Frazier[135] report 5 women who had aborted repeatedly and who presented no evidence of syphilis but showed definite serologic evidence of previous infection with Br abortus Carpenter[139] recently has isolated Br abortus from an aborted fetus of an estimated age of 45 days The source of the infection was not determined Whitehouse[140] has reported a case of abortion in the wife of a farmer whose stock was infected in which Br abortus was isolated from the uterine discharges following the abortion

Infection of the child in utero may occur apparently through the placenta Williams[141] reported such a case where in spite of this complication the pregnancy went on to term with delivery of a living child

DIAGNOSIS

The extreme variability of symptoms and the lack of a characteristic clinical picture render the diagnosis of undulant fever on clinical grounds alone one of great difficulty This is particularly true in the early stages of the disease However a singular lack of discomfort out of all proportion to the height of

among the most characteristic of the disease In the early stages headache, irritability, insomnia and general muscular pains are common, but the mental faculties usually are clear Marked depression is noted often with a declining temperature As the disease progresses peripheral neuritis is frequent, occurring in over 50 per cent of cases This may affect any nerve, but the sciatic, sacral, intercostal and peroneal are involved most frequently The neuralgic pains vary greatly in intensity at different times The acute pain disappears in one to two days but recurrence is liable to take place from any exposure for a period of months Delirium may occur in malignant cases The deep reflexes often are moderately increased Impairment of memory and neurasthenia are common, but complete recovery usually takes place

Special Senses — Blurring of vision and deafness are common but are not permanent Taste and touch are affected often A general cutaneous hyper esthesia may occur most marked over the feet

Joints — A characteristic complication occurring in about 40 per cent of cases is a peculiar transient arthritis in which the joints become swollen hot and extremely painful but without redness of the overlying skin This symptom comes on usually in the later stages of the disease The hip, knee, shoulder and ankle joints are involved most frequently but any joint may be affected Especially painful is involvement of the sacro iliac and vertebral joints The attacks come on suddenly and usually subside after 5 or 6 hours, although it is 3 or 4 days before all symptoms disappear The process usually is confined to one joint, although subsidence in one joint may be followed by an acute attack in another The specific organism is present in the joint fluid Complete re covery is the rule and suppuration rarely occurs although Kennedy[133] reported suppuration in the costochondral joint from which he obtained Br melitensis in pure culture Baker[134] has reported recently a remarkable case of inter mittent hydrarthrosis of the knees with repeated recovery of Br abortus from the joint effusion

Bones — Bone disease is rare Osteomyelitis may occur sometimes with x ray evidence of rarefaction and decalcification (Burnet[135]) Cignozzi[136] re ports two cases of hip joint disease in children due to Brucella infection which were clinically indistinguishable from tuberculosis Complete recovery occurred in 2 or 3 months

Muscles — Muscular atrophy and paralysis may occur as a late symptom in prolonged attacks Recovery although slow usually is complete

Genito urinary System — As the kidneys usually are unaffected there are no distinctive urinary findings except for the presence at intervals of the specific organism Albuminuria is found rarely During the febrile periods the urine is scanty and highly colored

Orchitis and epididymitis usually unilateral are not uncommon compli

Malaria — The presence of malarial parasites in the blood and the prompt response to quinine therapy distinguish the malarial fevers

Rheumatic Fever — Absence of leucocytosis and rheumatic nodules the rarity of cardiac involvement and lack of response to administration of salicyl ates differentiate undulant fever from this disease

Subacute Bacterial Endocarditis — In this condition there is often a history of tonsillitis or upper respiratory tract infection and signs of endocarditis appear with mitral murmurs petechiæ and other signs of infarction A leucocy tosis of 1 000–18 000 is present The infecting streptococcus may be isolated by blood culture

Septicemia (Pyogenic) — Usually a focus of infection can be found The polymorphonuclear leucocytes are increased absolutely or relatively Petechiæ and retinal hemorrhages are frequent The joints affected often suppurate The infecting organism may be demonstrated in blood cultures

Visceral Leishmaniasis — In regions where this disease is endemic the differentiation may be difficult Distinguishing features are the great enlarge ment of the spleen in this disease and the demonstration in the peripheral blood or by splenic puncture of Leishman Donovan bodies

Tertiary syphilis may cause prolonged continuous fever but can be differen tiated by history of initial lesion, signs of syphilitic infection and the Wasser mann test

Hodgkin s Disease — The Pel Ebstein variety of this disease with its re peated waves of remittent fever over long periods suggests the pyrexial curve of undulant fever, but in the former the skin lesions lymph node enlargement, dyspnea and cyanosis are distinguishing features Excision of a gland gives the diagnosis

Laboratory Diagnosis

There are few diseases other than undulant fever in which the physician is so dependent upon laboratory findings for a correct diagnosis Two procedures are of special importance the cultivation of the organism from the blood or other body fluid and the demonstration of specific agglutinins in the blood serum

Isolation of the Organism

This of course is conclusive proof of the presence of Brucella infection The organism may be obtained by direct cultural methods or if contaminated fluids or tissues are to be dealt with preferably by animal inoculation

1 Direct Cultural Methods — a Blood Culture — The specific organism

the fever, and the absence of physical signs are most suggestive As the disease progresses the combination of sweating aches constipation, asthenia, undulant temperature and relapses is found in undulant fever more often than in any other disease (Cantaloube)[14] It is essential to remember that any unexplained fever may be undulant fever and that the only accurate means of diagnosis is by laboratory examinations

Differential Diagnosis

The diagnostic problem presented by undulant fever is well expressed by the statement of Bassett Smith[6] that nearly every case of undulant fever has in its early stage been treated for malaria or some pyogenic disease before the correct diagnosis has been made

Typhoid and Paratyphoid Fevers — In the early stages of undulant fever the singular lack of subjective symptoms out of all proportion to the height of the fever, is in marked contrast to the prostration and apathy seen so frequently in typhoid Absence of rose spots may be an aid As the disease progresses the obstinate constipation profuse sweats and fleeting arthritides are distinguishing symptoms of undulant fever, and intestinal hemorrhage seldom occurs in this disease In doubtful cases blood cultures and agglutination tests readily distinguish the two conditions

Tularemia — In the so-called typhoidal form of this disease, with fever, absence of glandular enlargement and without evident site of infection, the diagnosis may be difficult particularly as the blood serum may agglutinate both Brucella melitensis and Pasteurella tularense Marked difference in agglutination titer determines the diagnosis but where practically equivalent titer exists, agglutinin absorption tests are necessary Cases of this type are found usually in laboratory workers who have been handling animals artificially infected with Pasteurella tularense The blood in tularemia shows moderate leucocytosis

Tuberculosis — In miliary tuberculosis distinguishing features are a history of existing tuberculosis, a rapid pulse out of proportion to the fever, a relative increase in the polymorphonuclear leucocytes dyspnea and cyanosis X ray examination of the lungs often gives the diagnosis Signs of meningeal involvement indicate tuberculosis and here spinal puncture generally will yield the tubercle bacillus In chronic cases of undulant fever the cough, night sweats, hectic fever and emaciation strongly suggest tuberculosis and such cases were described by early writers as Mediterranean phthisis, which yielded remarkably to treatment In children cases of Brucella hip joint disease have been described, which are clinically indistinguishable from tuberculosis X ray examination and laboratory tests serve to differentiate doubtful cases

cultures is increased by adding specific agglutinating serum to the urine before centrifugalization

c Stool Cultures — Cultural difficulties render this method valueless for diagnostic purposes Amoss and Poston[51], however have been able recently to isolate Brucella organisms repeatedly from the stools of undulant fever patients using a method of concentration by agglutination with specific serum before plating out cultures

d Splenic Puncture — Brucella organisms are present constantly in the spleen during the course of the infection, and some authorities have advised splenic puncture as the most certain method of diagnosis This procedure rarely is justifiable however as the organ is very soft and friable with capsule easily torn and fatal hemorrhage may result

e Other Sources — Although lactation is usually scanty in women suffering from undulant fever the specific organism frequently may be cultured from the milk The milk is spread on the surface of infusion agar plates and incubated as described above

The organism occasionally may be obtained by aspiration of joint fluids and abscess like swellings

Animal Inoculation — The presence of Brucella infection often can be demonstrated by animal inoculation when direct methods fail This is particularly true in the case of Br abortus (bovine) primary cultures of which are difficult to obtain The susceptibility of the guinea pig to Br abortus infection first demonstrated by Smith and Fabyan[9] has made it possible to obtain pure cultures of the organism from contaminated tissues and fluids by passage through this animal The inoculation disease in guinea pigs usually is non fatal and self limited A chronic infection is produced strikingly resembling tuberculosis characterized by the formation of small tubercle like foci in spleen liver lungs kidneys lymph nodes and epididymis, with swelling of carpal joints and ribs The spleen and lymph nodes are greatly swollen Suppuration usually follows in the epididymis Microscopically there is extensive proliferation of epitheloid and lymphoid cells followed by degeneration of the normal cellular elements Theobald Smith[66] believes that by the injection of small doses of recent strains the bovine and porcine varieties of Br abortus can be distinguished with reasonable certainty the latter causing more severe lesions with a tendency to suppuration in the lymph nodes and thymus Schroeder and Cotton[60] also consider this to be a differential point

The suspected fluid or emulsion of tissue should be injected intraperitoneally the guinea pig being weighed before injection and at necropsy, which takes place six weeks after inoculation Heart s blood should be taken for agglutination tests and cultures taken from the spleen and other organs incubating these both in ordinary air and in a 10 per cent carbon dioxide atmosphere

can be recovered frequently from the blood especially in the early stages of the disease Positive cultures have been obtained as early as the second and as late as the 300th day of infection In a series of 258 blood cultures in Malta, Eyre[53] reports successful cultivations of Br melitensis in over 65 per cent Shaw[143] found cultures were more apt to be positive if taken at the height of the evening pyrexial rise The organism usually is present in the blood in relatively small numbers and an adequate quantity of blood must be inoculated Special care must be taken to avoid contamination as Br melitensis grows very slowly and may be overgrown easily by any extraneous organism Various species of the organism differ in atmospheric carbon dioxide requirements, and if infection by Br abortus (bovine) is suspected it is important to make duplicate series of cultures one being incubated in ordinary air and the second in jars containing an atmosphere (by volume) of 10 per cent carbon dioxide

With a sterile syringe 10–15 c c of blood are withdrawn from a vein of the arm under strict aseptic precautions and inoculated at once, in amounts varying from 0 1 c c to 2 0 c c into a series of flasks containing 30 c c of fresh beef liver infusion broth pH 6 6 The remaining blood is divided between two sterile test tubes the blood allowed to clot the serum with its antibodies removed and each clot inoculated into a flask containing 50–100 c c of broth Successful cultures have been obtained from such clots, when whole blood has proved negative

The flasks are incubated at 37° C After the fourth day sub-cultures should be made daily from the bottoms of the flasks on peptic digest blood agar slopes or on Stafseth s infusion agar beef liver medium pH 6 6 (Huddleson)[1] The flasks should not be discarded as negative until after two weeks incubation If Brucella organisms are present they will appear in the sub cultures after 2–3 days incubation as minute dew drop colonies Cultures from these colonies then are tested morphologically, culturally and by agglutination with specific anti serum Even though the organism is thus identified as belonging to the Brucella group the problem of classification as to type remains to be solved This is determined through agglutinin absorption (Evans) guinea pig inoculation (Theobald Smith) and bacterial metabolic tests (McAlpine and Slanetz Huddleson) elsewhere described

b Urine Culture — Repeated cultures may be necessary, as the organism is frequently absent Kennedy[78] isolated Br melitensis in approximately 10 per cent of urine samples examined from undulant fever patients in Malta With repeated examinations, however, he was able to recover the organism in 72 per cent of a series of 43 patients The urine should be taken with aseptic precautions centrifugalized and the sediment spread over the surface of infusion agar or infusion agar beef liver plates which are then incubated for 10 days Where the organisms are few in number, the likelihood of obtaining positive

cultures is increased by adding specific agglutinating serum to the urine before centrifugalization

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Gilbert, Coleman and Groesbeck[144], in examining milk for presence of Br abortus, found guinea pig inoculation far more reliable than cultural methods

Serological Tests

Agglutination Test —The value of the serum agglutination reaction in the diagnosis of undulant fever was demonstrated first by Wright[11] in 1897, and upon this test, in the majority of instances, the recognition of the disease depends The test should be applied as a routine in all cases of unexplained fever In the blood serum of patients suffering from Brucella infection, the specific agglutinins may be demonstrated usually after the fifth day and occasionally on the first day Agglutinins usually are present in large amounts, reacting in dilutions of 1–100 or even 1–1000 in the first week of infection, and often rising later to very high titers (1–500 000, Eyre[83]) Durham found the rate of development of agglutinins varied inversely with the strength of the infecting dosage They persist in the blood long after recovery, occasionally as long as 10 years (Eyre)[83]

Technique —In performing the agglutination test, 3–5 c c of blood should be withdrawn from a vein of the arm placed in a sterile test tube and allowed to clot The serum then is removed and divided into two parts, one of which should be heated to 56° C to remove the non specific agglutinins Each serum should be put up with the bacterial emulsion by the macroscopic method in a sufficient series of dilutions 1–10 1–20 1–40, 1–80 1–160 1–320, etc, with control of known positive and negative sera Br abortus should be used as the antigen, on account of the danger of laboratory infection from Br melitensis variety melitensis The bacterial emulsion should be prepared from a stock strain of known agglutinability which has been grown on glucose agar for 48 hours killed by heating to 65° C for 30 minutes and made up by dilution into a stock antigen of a definite turbidity standard (Evans[145]) In performing the test 0 5 c c of antigen of a turbidity standard[146] of 1000 is added to each tube containing 0 5 c c of diluted serum The final antigen turbidity is therefore 1–500 Evans[145] properly has laid stress upon a constant density of the antigen, if the results of different observers are to be compared The tubes are incubated in a water bath at 37° C for 4 hours then removed to an ice box, where they are allowed to stand until the following day, when readings are made Only complete, or practically complete agglutination should be reported as positive

The agglutination titer which should be considered as diagnostic of undulant fever, is not generally agreed upon Bassett Smith[147] considers complete sedimentation at 1–30 as diagnostic Evans[145] regards complete agglutination in 1–40 dilution or lower as suspicious and in dilutions above 1–40 as good evi

dence of undulant fever past or present providing tularemia can be excluded Eyre[43] required a positive reaction at 1-30 or 1-50 for diagnosis preferably the latter Hardy[118] regards a titer of 1-40 as doubtful 1-80 as weakly positive 1-160 and above as positive Fici considered a titer of 1- 00 the minimum for diagnosis Evans[46] believes the discrepancies in the results of different workers can be explained by variations in technique the most important being in the density of the antigen used

Sources of Error —While the agglutination test usually gives reliable results certain sources of error must be kept in mind

a Absence of reaction is not proof of non infection Sometimes the reaction is delayed for weeks after the disease is well established Carpenter[44] reported a series of five patients yielding positive blood cultures of Br abortus in whom the sera of two contained no specific agglutinins Bassett Smith[117] observed three chronic cases with marked cachexia in whom the reaction was slow incomplete and only obtainable in low (1-10) dilution Cases have been reported in which no agglutinins have been demonstrable throughout the disease even against the actual strain of Brucella isolated from the patient

b Non specific reactions may occur in low dilutions in normal sera especially in cases of febrile disease These may be avoided by heating the serum to 56° C for 30 minutes as recommended by Negre and Raynaud

c Paradoxical reactions occur frequently in agglutination tests with the Brucella organisms In this phenomenon the cause of which is not definitely known certain dilutions of serum may give a negative reaction while higher dilutions are strongly positive This zone or phase of no reaction has been variously termed an inhibitory zone proagglutinoid zone or prezone Diagnostic errors from paradoxical reactions may be avoided by using a sufficient series of serum dilutions in the performance of the test Bassett Smith[75] advises at least three dilutions 1-40 1-100 and 1-400

d Paramelitensis and para abortus In regions where paramelitensis or para abortus infection exists as in the Mediterranean littoral the serum to be tested must be agglutinated against these antigens as well as the standard antigens In the United States this source of error is practically non-existent since but one paramelitensis variety a porcine strain from Missouri (Evans[14]) has ever been isolated in this country

e Cross agglutinins Francis and Evans[49] working with 100 sera from human cases of tularemia found 37 that showed cross agglutination for Br melitensis and Br abortus as well as for Bact tularense and that in 3 instances the agglutination titer was the same for the three organisms In like manner 3 of 8 undulant fever sera cross agglutinated B tularense but the agglutination titer was low Brucella and B tularense infections were easily differentiated however by agglutinin absorption tests These observers con-

clude that sera of patients suspected of undulant fever or tularemia should be tested for agglutinins of both organisms unless the clinical history definitely points out the source of infection If the difference in serum titer is marked, the diagnosis is determined usually by the higher titer, if the titers are approximately the same agglutinin absorption tests must be performed

Complement Fixation Test — Brucella infection in man and animals causes the formation in the blood of complement fixing amboceptors, and the complement fixation test gives results comparable to the agglutination reaction The test is too complicated, however for general use

Intradermal Tests — Meyer and his associates[150] in 1918 demonstrated that infection of guinea pigs with Br abortus always produced cutaneous hypersensitiveness and that a positive intradermal test was a reliable index of infection in these animals Controls and also animals immunized with killed cultures of Br abortus invariably were negative The characteristics of the positive reaction were marked induration frequently with central necrosis, with persistence of the reaction over 48 hours In 1919 they[151] obtained similar results using both Br abortus and Br melitensis as infecting organisms In 1922 Burnett[152, 153] applied the intradermal reaction to the diagnosis of undulant fever in man He found the agglutination reaction negative in 15–20 per cent of human cases of undulant fever but in these cases the intradermal test gave positive results He performed the test by the intradermal injection of 0 1–0 5 c c of broth filtrate of killed Br melitensis (melitine) or Br abortus (abortine') In about 6 hours in positive cases a local reaction appears with edema and redness which lasts several days Burnet obtained positive results in cases of undulant fever from the eighth day onward Other workers as Mitra[154] and Bua[155] prefer intradermal injections of killed Brucella organisms suspended in salt solution In the United States Giordano[156] found broth filtrates of Br abortus unsatisfactory but when salt suspensions of heat killed Br abortus were injected intradermally specific local reactions occurred in known positive cases of undulant fever while controls were negative The intradermal test does not distinguish between the different varieties of Brucella

PROGNOSIS

The prognosis of undulant fever in so far as life is concerned is good but in view of its protracted course and resultant invalidism the disease must be regarded as more serious than the death rate would indicate The average case mortality in the British Army and Navy in Malta for seven years prior to 1908 was 2 3 per cent In the civil population of Malta however, for the same period the case mortality was much higher 10 5 per cent (Eyre[93]) Death occurs as a result of severe toxemia with hyperpyrexia heart failure or pulmonary

complications *Hughes*[117] *in an analysis of 45 fatal cases in Malta found that 60 per cent* died in the first month of illness but it must be emphasized that a severe relapse accompanied by malignant symptoms may develop at any stage of the disease Unfavorable symptoms are continued fever of 104 F or above a dry brown tongue intermittent pulse pneumonia delirium or severe diarrhea Hughes found it impossible to fix a period after which the patient becomes proof against relapse but observed that subnormal temperature for several days if accompanied by a clean tongue and general mitigation of symptoms usually indicates approaching convalescence

Birt and Lamb[17] found that repeated quantitative estimations of the serum agglutinins were of considerable value in prognosis A persistently high and rising agglutination curve was favorable Persistently low agglutination titers or a high titer succeeded by a falling curve were unfavorable and indicative of a protracted illness These findings have been confirmed by Bassett Smith[6] Manson Bahr and Willoughby[48] however found the titer of agglutination to be without bearing on the prognosis

Prophylaxis

With the recognition of its widespread and apparently increasing incidence the prevention of undulant fever has become a public health problem of great importance As infected milk and milk products are the principal sources of the disease adequate protection must be given to the milk consumer The organism is readily killed by pasteurization and this procedure should be adopted more widely That sterilization of milk will prevent undulant fever in that major section of the population which has no direct contact with infected animals was shown strikingly by the prompt and almost complete disappearance of the disease from the British military and naval forces in Malta following the prohibition of the use of unboiled goats milk in 1906 Among the civil population of Malta which stubbornly refuses to recognize any connection between the use of unboiled goats milk and undulant fever the incidence of infection remains high Avoidance or sterilization of milk products further resulted in an almost total absence of undulant fever in the large military forces employed in the Mediterranean area during the World War although the disease was prevalent in the civil population In the large cities of the United States where a high percentage of the milk supply is pasteurized the disease is relatively rare

The problem is far more difficult however in that portion of the population having close contact with live stock where contact infection is a frequent source of the disease Pasteurization of milk in rural communities seldom is practicable and the prevention of undulant fever on the farms small towns

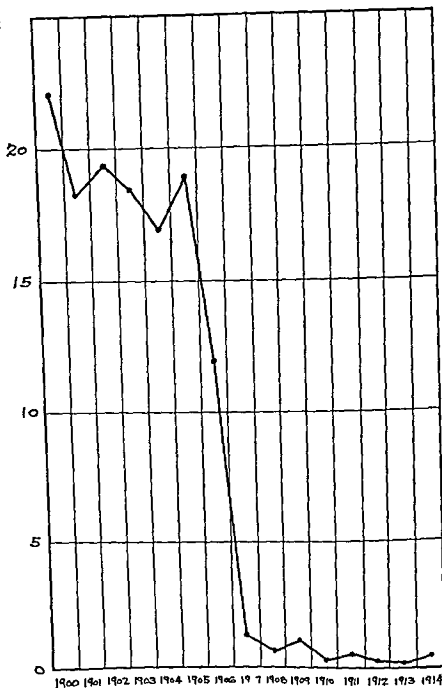


Fig 5 Showing marked reduction of incidence of Undulant fever in Mediterranean squadron (British Navy) following prohibition of use of unboiled goats milk in 1906 (after Stephens)

and among packing house workers is largely dependent upon proper precautions on the part of those handling live stock or carcasses and especially upon control

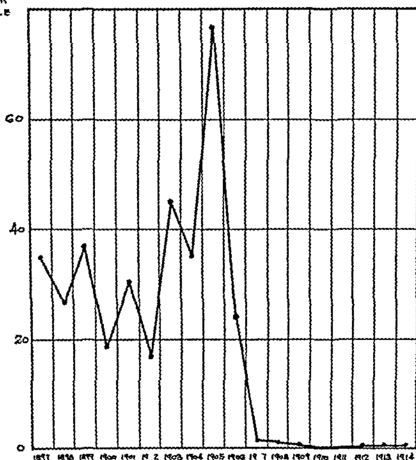


Fig 6 Showing marked reduction of incidence of Undulant fever in Malta Garrison (British Army) following prohibition of use of unboiled goats milk in 1906 (after Stephens)

of the infection in animals The magnitude of this undertaking is shown by the fact that Br abortus infection in cattle is present and in high incidence throughout the United States with the infection also common among swine in the states of the Middle West and among goats in the Southwestern states

The control of the disease in cattle and goats has been attempted by means

of vaccines using both killed and living cultures The results with killed cul tures have not been encouraging Living cultures of Br abortus appear to have some prophylactic value, but this procedure may be dangerous, as the animals thus infected may become chronic carriers of the disease and may ex crete virulent organisms in the milk for long periods

In recent years much has been accomplished in the eradication of Br abor tus from dairy herds by the systematic removal of all infected animals with the ultimate object of building up non infected herds Birch and Gilman[1 9] recommend the periodical testing of all members of the herd by means of the agglutination test with segregation of all infected cattle By cooperation on the part of the herd owner with the veterinarian and with the assistance of adequate laboratory facilities, this plan has been used successfully and sound herds thus built up Constant care must be taken however, to avoid reintro-duction of infection into the herd through the purchase of infected animals

In Malta, an effort has been made to examine systematically all milch goats and to destroy those found infected Though the incidence of undulant fever in Malta has been reduced considerably in this manner, the lack of an adequate inspection staff has limited the extent of herd purification (Zammit[94])

Prophylactic vaccination in man has not been attempted on a scale sufficient to determine its true value but the results have not been encouraging Birt and Lamb[157] reported the attempted immunization of a man by three prelimi nary subcutaneous inoculations of killed cultures of Br melitensis Subsequent inoculation of a small quantity of living culture was followed by an attack of undulant fever which ran a characteristic course Eyre[1 4] in experiments upon rabbits found that long continued treatment by injection of killed cultures of Br melitensis produced a high agglutination titer in the blood, but subsequent introduction of even comparatively small amounts of living virulent cultures almost invariably caused the death of the animal Eyre[160] in 1906 attempted the immunization of 51 hospital attendants in Malta but the results were in conclusive Nicolle and Conseil[161] administered killed cultures of Br melitensis, both orally and by subcutaneous inoculation and found that a considerable degree of immunity was obtained Burnet[63] has used living Br abortus as a vaccine against Br melitensis infection and finds that a single inoculation will protect man and the monkey against a dose of Br melitensis which invariably caused active infection in controls

Disinfection of the urine and stools of undulant fever patients should be carried out systematically as large numbers of virulent organisms often are excreted through these channels Contact infection from human cases how ever apparently is not common This is not easy to explain when the frequency with which Br melitensis infects laboratory workers is considered Laboratory infections can be avoided by the use of Br abortus cultures for laboratory and

diagnostic purposes as recommended by Burnet instead of the more virulent *Br melitensis* Human carriers of the type first noted by Shaw should not be permitted to handle food supplies

Treatment

Undulant fever is a self limited disease of uncertain duration and is but little affected by specific therapeutic measures The large number of remedies which have been advocated in the past is indicative of their slight therapeutic value In a prolonged illness in which marked remissions or even spontaneous recovery may occur at any time it is difficult to judge the value of any particular form of therapy The general therapeutic indications are prolonged rest maintenance of nutrition and symptomatic treatment as required

General Care —The patient should be isolated and all excreta disinfected The sick room should be sunny well ventilated with an even temperature and a comfortable bed In such a prolonged debilitating illness a trained nurse is essential Light woolen bed clothing will be found advantageous as it absorbs perspiration avoids chilling and may lessen the frequency of the rheumatic pains The mattress should be protected by a rubber sheet and the bed clothing and linen should be changed whenever they become damp The patient should remain in bed constantly during the acute stage until the temperature has been normal for at least ten days and a clean tongue and subnormal temperature indicate permanent improvement Many relapses can be traced to allowing patients to get up too soon The teeth should be kept clean and a soothing mouth wash prescribed

Diet —The diet is important and the patient s strength and nutrition should be maintained by giving him as much food as can be assimilated Hughes[117] and others have laid stress on the appearance of the tongue as a guide to the state of the gastro-intestinal mucous membrane and as an index of the patient s digestive powers With a fairly clean tongue and moderate fever a more liberal diet can be given In the acute stage the diet should be liquid as milk albumen water fruit juices and egg nogs Later fresh fruits cooked cereals vegetable purees eggs custards chicken and fish may be added The patient should be urged to take water freely at all times In chronic cases with anemia and impaired digestive function the maintenance of nutrition often is difficult

Hydrotherapy —The fever is best controlled by hydrotherapy A warm cleansing bath should be given each morning For a temperature of 103 F a tepid or tap water sponge should be given and for a temperature 104° F or over a cold sponge or wet pack may be required Slight friction when drying the patient is beneficial These measures keep the skin in good condition

improve the circulation, quiet the nervous irritability and promote general metabolism Bassett Smith [6] cautions against checking the profuse sweats by hydrotherapy

Treatment of Special Conditions — Constipation is a marked feature and should be treated with mild laxatives as liquid petroleum, cascara or licorice powder supplemented by enemata if necessary A bed pan should be used in the acute cases later, a closed stool Headache is relieved by the use of an ice cap Nervous irritability may be benefited by bromides or small doses of luminal Persistent insomnia may require occasional mild hypnotics Arthritis is best treated by hot applications or radiant heat and light The chronic cases with neuralgia or neuritis are benefited by conservative physiotherapy, including radiant light or cabinet baths and galvanism Wasted muscles should receive light daily massage and electrical treatment using the sinusoidal current Morphine should be avoided as a habit is easily induced in a prolonged illness of this character The anemia should be treated by suitable diet, and the administration of iron in the form of Blaud s pills or occasionally by intramuscular injections of iron or arsenic

Convalescence — During convalescence the patient should be encouraged to take gentle exercises out of doors if weather is suitable He should be warmly dressed and cautioned against over exertion or exposure, which are apt to bring on a relapse Change of climate often accelerates recovery

Chemo therapy — No drug has been found as yet which has a specific value in treatment with the possible exception of sulfanilamide Intravenous injections of mercurochrome have been reported as curative but the evidence is not conclusive (Ross and Martin[167]) Izar and Mastroeni[163] and Hoffman[164] have treated cases with intravenous injections of acriflavine with apparent benefit

Sulfanilamide in customary dosage (see Vol IV Chapt XXX-A) appears to have considerable value in the treatment of undulant fever Its use in single or small groups of cases has been discussed recently by several authors ([174–194]), all claiming good results in the great majority of patients as a rule, these have been cases of rather short duration Neumann[195] has reported 20 patients with satisfactory results in 17 Not infrequently a relapse has followed discontinuance of the drug with cure following a second course of sulfanilamide It is fair to state that with its varying course undulant fever is a disease in which it is particularly difficult to evaluate therapy but the reports indicate better results from sulfanilamide than from other therapy

Vaccine Therapy — This has been used in a number of instances without apparent benefit Bassett Smith however whose experience has been very extensive considers vaccine treatment the most valuable form of therapy which we possess in undulant fever From a series of 61 cases treated at the Haslar hospital in Malta with stock melitensis vaccine he[165] concluded that in acute cases with much auto infection little or no good was derived from vaccines, but

that in the more chronic forms with irregular or slight temperature there was distinct benefit The constitutional reactions were slight and transient In no case was abscess formation noted at the site of inoculation although the development of *small hard subcutaneous nodules apparently due to local irritative* action was observed frequently These disappeared in a short time A rise in both opsonic index and agglutination curve was noted, accompanied by improvement of symptoms and shortening of the course of the disease More recently this investigator[8] has recommended the use of sensitized vaccines, using an autogenous vaccine if possible if not a polyvalent vaccine made from many strains The initial dosage advised is 100 million organisms and this is increased to 250–500 millions the injections being given at 5–7 day intervals until the patient is immunized The dosage should be in inverse ratio to the temperature and vaccines should not be given if the temperature is high Kennedy[19] recommends smaller doses of vaccine 6–9 million at intervals of 2–4 days De Finis[166] has also reported good results from vaccines in a series of 55 cases Angle[167] has reported recently a series of ten cases of undulant fever due to Br abortus in which distinct benefit was obtained from abortus vaccines An indurated area considered to be allergic developed at the site of the inoculation which was slow to disappear Simpson and Frazier[155] also consider Br abortus vaccines of value Wainwright[77] reports a case in which vaccine treatment was attempted but discontinued because sterile abscesses were produced regularly at the site of inoculation

Non specific protein injections have been found occasionally effective Awe and Palmer[168] treated three cases with injections of 5–10 c c of sterile milk with prompt recovery in all although these observers point out that the injections were given relatively late in the course of the disease when spontaneous recovery might be expected

Serum Therapy —Wright[169] in 1895 attempted to produce an anti serum for therapeutic use by injecting goats with killed cultures of Br melitensis This serum possessed little agglutinative power and in experimental infections in monkeys exhibited neither protective nor curative properties In 1896 Wright[169] produced a horse anti serum by similar methods which was used later by Aldrich[170] in the treatment of five cases of undulant fever with some apparent benefit In 1903 Eyre[124] attempted the production of a bactericidal serum using rabbits guinea pigs goats and lastly a horse His results were not encouraging The rabbit and goat serum appeared to possess no therapeutic value whatever The horse serum although possessing an agglutinative titer of 1–3000 did not prevent infection in other animals even when given in large amount and was without value in the treatment of infected guinea pigs monkeys or in one case of human undulant fever However when 0 1 c c of serum and a standard dose of Br melitensis were inoculated simultaneously into the cerebral tissues of guinea pigs the animals remained unaffected

Trambusti and Donzello[171], however, have reported encouraging results from the use of a therapeutic serum prepared from goats and Negre and Sergent[17] report benefit from the use of a polyvalent serum, provided it contains a strain of the same type as the infecting organism Voge[173] recently has found the serological changes which occur in cattle following injections of Br abortus to be associated with the serum euglobulin fraction In experimental work upon rabbits serum euglobulin obtained from anti abortus cow serum appeared to give protection to a rabbit subsequently infected with Br abortus, while serum euglobulin from normal serum did not give this result

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CHAPTER XXV-A

RELAPSING FEBRILE NODULAR NONSUPPURATIVE PANNICULITIS (WEBER CHRISTIAN DISEASE)

By HENRY A CHRISTIAN

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Definition — A rare disease of unknown etiology relapsing in type characterized by prolonged irregular fever multiple quite large sub cutaneous nodules in the panniculus adiposus and sometimes in other adipose tissue the former of which heal with atrophy to leave depres sions in the skin

Incidence

In addition to the three instances of this disease reported up to 1928 the first by Gilchrist and Ketron[1] under the title a unique case of atrophy of the fat layer of the skin preceded by the ingestion of the fat by large phagocytic cells macrophages the second by F Parkes Weber[2] using the term relapsing nodular nonsuppurative panniculitis showing phagocytosis of subcutaneous fat cells by macrophages and the third by Henry A Christian[3] adding to Weber s chief terminology the word febrile 35 other cases can be found in the literature

All three of the first patients were female while of all reported cases 7 per cent have been female[4] Age has ranged from 23 months to 64 years with of 38 cases 6 in the 20 9 age group 11 in the 30 39 group 5 in the 40 49 group and 9 in the 50 59 group

Without any prodromata or indefinite ones for two to four weeks the patient notes the appearance of lumps under the skin with some reddening over them. They are tender rather than painful. They may be single, few or many. Later in the author's patient after a month fever associated with headache, nausea, vomiting, muscle pains and slight arthralgia and slight cough appeared. This is the usual happening. During the fever new lumps appear. The fever is of an irregular type (see Chart I) ranging from 99° to 106.4°F. There may be chills. The fever may continue for several weeks to recur after varying periods of freedom. It has lasted as long as 115 days. In the author's patient there were ten recurrences in a ten year period. In another patient recurrences have developed over a period of fifteen years.

As the process heals there is atrophy of the involved adipose tissue causing depressions in the skin, some as large as 5 by 7 cm in diameter and giving a curious appearance to the involved parts as shown in the accompanying photograph (Fig. 1). Pigmentation may appear at the site of nodules.

The blood shows a slight leukopenia, 3000 white blood cells in one febrile period and 3800 in another in the author's case; lymphocytes show a moderate relative increase. Occasionally a moderate polynuclear leucocytosis develops. Red blood cells and hemoglobin are very slightly decreased. Urine is normal. Basal metabolic rate is normal. Physical examination except for the subcutaneous lesions is normal except that in three patients an enlarged spleen has been found.

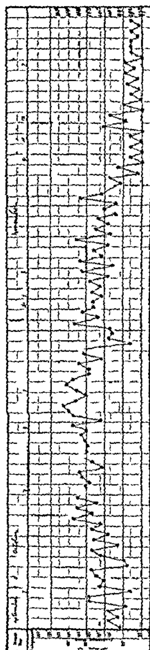


CHART 1 — Temperature curve during the fifth attack of relapsing febrile nodular nonsuppurative panniculitis.

Etiology and Pathology

There is no proved etiology Cultures from the nodules and from the blood stream have been negative Animal inoculations have been negative in result Microscopic examination of excised nodules, stained in various ways have revealed no micro-organisms and no inclusion bodies suggestive of a virus cause The type of fever with relapses is suggestive of undulant fever unfortunately no agglutination tests have been made on the serum of these patients for organisms of the undulant fever (Brucella) group In the earlier stages there is considerable resemblance to erythema multiforme or erythema nodosum but it differs from these both in the histological appearance of the lesions and in the subsequent course with atrophy of the subcutaneous adipose tissue A possible relationship to dermatomyositis has been suggested

The lesions are felt beneath the skin as irregular, poorly defined, slightly tender nodules Microscopically they show infiltration of the connective tissue between and about the fat cells with lymphoid plasma young connective tissue cells and endothelial cells phagocytic for fat droplets Polymorphonuclear cells are sparse Some foreign body giant cells are seen Blood vessels beyond congestion show but little Rarely a slight degree of peri- or end arteritis has been noted The fat tissue often is edematous In places there is necrosis of the fat cells, and fibrin threads are seen No fatty acid crystals appear There is a varying degree of infiltration in the connective tissue septa

The process does not involve the dermis As the lesions heal the fat tissue atrophies and depressions in the skin surface result These lesions vary in size from one half to several centimeters in diameter They are most numerous on the extremities but are present too on the trunk None have been noted on the head palms of the hands or soles of the feet The following locations have been found thighs [illegible]8 legs 25, arms [illegible] trunk [illegible]2, buttock 2 breast 2 feet 1 and face 1 Rarely a nodule undergoes necrosis and may discharge a grayish amorphous material

In the body apart from the panniculosus adiposus inflammatory lesions like those of the skin have been found in the fat tissue of the body cavities and the liver has shown fatty infiltration and areas of necrosis

Symptomatology and Clinical Course

Although a very rare disease its clinical picture and course is so striking as to merit brief description

Without any prodromata or indefinite ones for two to four weeks the patient notes the appearance of lumps under the skin with some reddening over them. They are tender rather than painful. They may be single, few or many. Later in the author's patient after a month fever associated with headache, nausea, vomiting, muscle pains and slight arthralgia and slight cough appeared. This is the usual happening. During the fever new lumps appear. The fever is of an irregular type (see Chart I) ranging from 99° to 106.4°F. There may be chills. The fever may continue for several weeks to recur after varying periods of freedom. It has lasted as long as 115 days. In the author's patient there were ten recurrences in a ten year period. In another patient recurrences have developed over a period of fifteen years.

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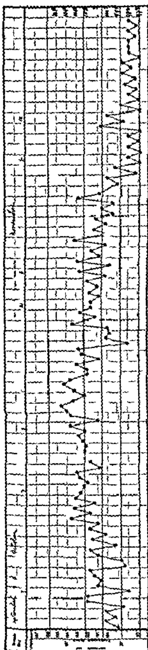


CHART 1 — Temperature curve during the fifth attack of relapsing febrile nodular nonsuppurative panniculitis.

No complications and no sequelae except the areas of atrophy of subcutaneous adipose tissue develop



FIGURE 1 — Deep irregular depressions in the cutaneous surface of the legs of a patient suffering from an attack of relapsing febrile nodular nonsuppurative panniculitis (Christian's case)

DIAGNOSIS AND TREATMENT

Diagnosis is obvious from the history, clinical course and subcutaneous nodules and/or areas of atrophy

Treatment should be supportive and symptomatic A variety of drugs such as atabrine quinine *antimony, arsphenamine, sulfathiazole* sulfapyridine sulfadiazine and penicillin have been tried without any significant effect In one patient potassium iodide caused a flare up

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July 1 1950

CHAPTER XXVI

PERTUSSIS

(Whooping Cough)

By WILLIAM PALMER LUCAS

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INTRODUCTION

Definition—Pertussis or whooping cough is an acute contagious disease in which the infection is transmitted almost entirely by direct contact through droplet infection The primary seat of the infection is in the respiratory tract and the early course of the disease can scarcely be differentiated from any ordinary respiratory tract infection The later stages, however are characterized by the well known inspiritory whoop and are recognized easily even by the layman

De Baillous in 1578 gave the first adequate description of the disease Since the XVII Century numerous epidemics have been described and the symptomatology has become well known However it is only since Bordet and Gengou[1] described the organism in 1900 and since the characteristically brilliant work of Mallory[2] in 1912 described the specific pathology of the upper respiratory tract that we have acquired a comprehensive knowledge of the disease The disease is an acute general and specific infection of the respiratory tract with an

pertussis must be recovered from the experimental animals and must be identified bacteriologically and serologically

Williams carried out a careful bacteriological study in the research laboratory of the New York City Health Department Most of her cases were patients in the early stages of the disease The laboratory findings were abundant and in most cases a pure culture of a bacillus was found which corresponded to the bacillus described by Bordet and Gengou[1] A number of strains were isolated which were distinct from the hemoglobinophilic bacilli and from bacilli morphologically similar to the Bordet Gengou bacillus In the laboratory these strains isolated from whooping cough cases were able to produce complement fixation tests in inoculated animals It is believed that these strains are different varieties of the same bacillus

Povitzky and Worth[3] thought they could prove the presence of *Hemophilus pertussis* by agglutination and complement fixation tests and succeeded in differentiating the typical pertussis bacillus from the influenza bacillus as well as from other organisms including the *B bronchisepticus*

At present the consensus among bacteriologists pathologists and serologists seems to be in favor of accepting the Bordet Gengou bacillus *Hemophilus pertussis* as the specific causative organism that produces the clinical disease known as whooping cough

Pathology

Our knowledge of the pathology of pertussis has been strengthened greatly by the histological and experimental work done by Mallory and his associates[5] who made a microscopic study of the trachea and lungs of three patients who had died early in the course of an attack of whooping cough They described a lesion which involved the ciliated epithelium lining the trachea and bronchi Between the cilia of the epithelial cells were packed a great number of minute bacilli In many cases the cilia had disappeared almost entirely or remained only as stumps The lesions were not always uniformly distributed throughout the lungs The ciliated epithelial cells lining the ducts of the mucous glands running to the trachea were found involved also in one case There was quite an increase in the polymorphonuclear leucocytes and these had large numbers of organisms included in their cytoplasm Beyond this injury to the cilia the reaction of the tissues to the bacilli was moderate Apparently there is not so much an increase in the secretion of mucus

initial fever However, in many cases the elevation of temperature above normal is so slight that it may be unnoticed The blood reaction also shows the specificity of the infection by the presence of a characteristic lymphocytosis and the development of immune bodies

Etiology

In 1900, Bordet and Gengou[1] described a new bacillus which they had found in a case of whooping cough They were not able to isolate it in pure culture until 1906 The bacillus they described was small ovoid and gram negative growing with difficulty in the early generations except on a special potato blood agar medium, later generations growing with much less difficulty even on plain glucose agar

In the early period there was considerable dispute as to whether this organism really caused whooping cough Many of the earlier negative reports were studies on late cases where very frequently there is no pure culture of any bacillus and where the predominating organism usually is the influenza bacillus *Hemophilus influenzae*, frequently found in the later stages of many respiratory tract infections It is easy to explain the lack of constant findings with an organism difficult to isolate and grow such as the *Hemophilus pertussis* bacillus especially when most of the examinations are made late rather than early in the course of the disease However meticulous workers have been able to find it when working under favorable conditions with early uncomplicated cases and proper media

Individual workers have been able to confirm Bordet and Gengou's[1] findings Mallory Horner and Henderson not only isolated the organism in pure culture but also described the specific biological reactions of *Hemophilus pertussis* on the blood of whooping cough patients The organism was obtained from the trachea and lungs Mallory Horner and Henderson also reproduced the condition in monkeys and puppies who developed all the symptoms of whooping cough except the whoop They described also the complement fixation test with this organism and the blood of the experimentally immunized animals By this cycle of proof it was shown that *Hemophilus pertussis*, the bacillus of Bordet and Gengou is the etiological factor in whooping cough

Rhea[8] has called attention to similar lesions produced by the *Bacillus bronchisepticus* and points out the necessity for careful interpretation in experiments carried on in dogs guinea pigs and rabbits *Hemophilus*

Also the difficulty of differentiating between whooping cough and some of the acute bronchial infections or from parapertussis tends to decrease the accuracy of statistics of the incidence of whooping cough

However there is no doubt in the mind of anyone that before the days of prophylactic immunization the disease was epidemic and sometimes pandemic This is brought out clearly by the writer's experience in San Francisco California where whooping cough was epidemic until immunization was practiced simultaneously by all of the pediatricians The San Francisco Public Health Reports now show practically no cases except those introduced from the outside This is particularly true since the Board of Health adopted prophylactic immunization against whooping cough in the well baby clinics on May 7 1943

That prophylactic immunization reduces the incidence of whooping cough to an extremely marked degree is borne out by the carefully accumulated statistics of Garvin[10] In Shaker Heights Ohio beginning in 1936 approximately 75 per cent of the preschool children were immunized at or before one year of age The children in adjacent Cleveland were not immunized in this thorough manner Garvin's report published in 1940 shows that for the period 19 9 to 1935 Cleveland's incidence of whooping cough was 167 5 per 100 000 population while Shaker Heights had an incidence of 89 5 From 1936 to 1939 the test period Cleveland's incidence remained at 167 5 while Shaker Heights with its immunization program dropped to 48 5 per 100 000 population and most of these cases were introduced from the outside Other communities who have carried out similar procedures have had the same favorable reduction in incidence

Sex Incidence — Authorities are unanimous in stating that whooping cough is the only contagious disease which shows a constant variation in sex incidence Girls are affected more often than boys Luttinger and Olmstead[11] in a tabulation of 8 5 0 cases found that the incidence according to sex was 44 8 per cent boys and 55 2 per cent girls The disproportion between the sexes extends into the adult age level in an even more marked manner In the age group over 15 years 87 per cent of the cases were females while only 13 per cent were males This preponderance of adult females may be accounted for in part by the fact that women are intimately exposed far more often than men

Seasonal Incidence — One would expect to find whooping cough more prevalent during the fall and winter months when upper respiratory tract infections are most common Such however is not the case Pertussis is more prevalent during the spring and summer Luttinger and Olm

as there is a mechanical interference of the movement of the mucus by the destruction of the cilia When the normal ciliary action is destroyed or diminished, the removal of secretions and the inhalation of foreign bodies produce the irritation which causes the characteristic spasmodic cough Mucus is freed from the denuded epithelium with difficulty, and because the cough depends on the accumulation of mucus, it becomes more or less periodic Colonies of the non motile *Hemophilus pertussis* become thick mucoid and tenacious on solid media This characteristic probably makes the bacilli adhere to the epithelium and stumps of the cilia and also partly accounts for the difficulty in dislodging the mucus

In cases of whooping cough there is a steady increase in the circulating blood of leucocytes particularly lymphocytes, as the paroxysmal wave increases and a steady decrease as the wave declines This change from the normal blood count usually lasts from one to two months The typical lymphocytosis is interfered with in complicated cases at which times a polymorphonuclear increase may be noted At the height of the disease the white count varies from 15 000 to 30 000 and on occasion may reach 100 000 or more The lymphocytes usually are from 80 to 90 per cent of that number

The following facts indicate that toxins are formed (1) there is an exudation of leucocytes into the trachea and bronchi from the surrounding blood vessels (2) there are moderate but definite changes in the lymph nodes of the spleen and of the gastrointestinal tract, (3) there is a definite increase in lymphocytes in the blood which is characteristic and specific enough to act as an aid in diagnosis, (4) there is a production of antibodies in the blood of patients and of experimental animals which can be discovered by complement-fixation tests and/or by agglutination reactions, (5) a definite immunity is derived from an attack of whooping cough

It has been suggested that a neurotropic toxin is present also, which affects the vagus and respiratory centers becoming fixed in the nervous tissue While this would in some cases seem a logical explanation it is difficult to prove because of the secondary infections particularly virus infections which give evidence of selective neurotropic action

Incidence and Epidemiology

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The typical paroxysm may be induced in a variety of ways Any emotional upset such as produced by an examination of the throat usually will succeed in bringing on the paroxysm as will laughing crying anger a sudden noise, a draught of air a glass of cold water or solid food The paroxysms also occur spontaneously especially at night Children usually have a premonition of the oncoming paroxysm This can be noted even in a small baby who will become restless and anxious before the coughing begins An older child will run to his mother or take hold of something solid for support A sleeping child will awaken sit upright and take hold of the sides of the bed before he begins to cough Older children have described a tickling or scratching in the throat or a choking or suffocating feeling Then will begin a forcible effort to clear the throat with rather short hacking expiratory efforts in which all the accessory respiratory muscles are used During this effort the child often presents a startling picture The face becomes suffused almost cyanotic the eyes project and become suffused and as the attack progresses hemorrhages may occur in the conjunctivae After several such agonizing efforts to remove the mucus in the throat there comes a deep inspiratory crowing sound caused by the air being drawn in through the narrowed glottis This succession of hacking cough and inspiratory whoop may be repeated until the child is almost exhausted The attack usually stops either with vomiting or by the expulsion of a small amount of thick tenacious mucus Sometimes during the paroxysm there is an involuntary passage of urine or feces due to increased abdominal pressure At times between the paroxysms there may be a short interval of quiet breathing The paroxysms however do no let up until the irritating mucus is brough up and this may take as long as from two to five minutes

The after effects of a complete paroxysm vary with the strength of the patient Strong children often will continue their meal or play as though nothing very serious had occurred whereas a weaker child will be exhausted covered with perspiration and have an increased respiratory and pulse rate If there are no complications the subjective feelings of the child usually are better during this second paroxysmal stage than they were during the first catarrhal stage when the irritating cough was more or less constant

The second stage usually passes through three phases The first phase is the period during which the number and intensity of the attacks increase it lasts about one week The second phase is called the acme and the paroxysms remain at their maximum frequency and in-

stead[11] in a careful analysis of 6 868 cases show that the greatest number of cases were reported between the months of May and September

Environmental Factors —All statistics prove the obvious fact that surroundings play their part in the incidence of pertussis with the congested localities having the highest morbidity MacKenzie[1] in his study Child in the One Room House", gives conclusive evidence of the effect of congested living

Racial Incidence —Pertussis is common to all races In the United States the American Indian according to Crim[9] has the greatest attack rate A higher rate is found in the colored races than in the white race during the age period under five years when whooping cough is most contagious

Not only the incidence but also the severity and mortality depend a great deal on whether the disease has been prevalent over many years When any new infection is introduced into a community the morbidity and mortality rate is much higher This is brought out clearly in reports from different areas in the Pacific where measles had not been known until it was introduced by the white man In many instances the spread was almost universal and the mortality was often as high as 20 to 40 per cent of the total population

Symptomatology[13, 14]

The period of incubation is given variably as from 3 to 15 days Usually the first symptoms to appear such as anorexia headache disturbed sleep and malaise are so mild that they are scarcely noticeable and it is difficult to set the exact date of onset

The first really definite signs are those of an acute catarrhal involvement of the upper respiratory tract A dry catarrhal type of cough which is not at first spasmodic together with sneezing conjunctival irritation and sometimes slight fever are the earliest symptoms

During the first week most of the symptoms except the cough disappear almost entirely The cough nearly always progresses In children who are subject to upper respiratory tract infections there may be intermittent attacks of acute laryngitis or croup When these later symptoms clear up the cough persists is more frequent at night and gradually assumes a choking or spasmodic form The typical whoop is rarely heard before the end of the first week more often it is not heard until the end of the second week

complication may be loss or disturbance of hearing sight or speech cerebral paralysis hemiplegia diplegia or monoplegia There may be meningeal complications meningeal hemorrhages or encephalitis The spinal fluid usually is normal but may be increased in pressure and there may or may not be a slight increase in the cells mainly lymphocytes The globulin and sugar content of the spinal fluid rarely are disturbed during these cerebral complications A lumbar puncture does not always give diagnostic evidence of meningeal involvement but in some cases may act as a favorable therapeutic agent These complications usually are accompanied by a rise in temperature an increased blood count stiffness of the neck a positive Kernig s sign and often delirium

The cerebral involvement may be ushered in suddenly with convulsions and often follows upon a series of acute paroxysms In many instances preceding the onset of convulsions there may be a period of 4 to 48 hours of lethargy during which time the patient becomes irritable when disturbed Following this there is twitching of the face or perhaps of the hand and shortly thereafter a generalized convulsion occurs Convulsions may be continuous and if so are often fatal in 6 to 8 hours death sometimes being preceded by a coma

Factors predisposing to convulsions are (1) age of the patient generally under two years and particularly under nine months (2) cyanosis due either to severe paroxysms or to the presence of bronchopneumonia (3) congenital brain defects

In a study made by Habel and Lucchesi[19] the brains of 7 patients who died following convulsions showed no specific pathological change pointing to an inflammatory lesion to account for the convulsions There were changes which could be attributed to an insufficient blood supply and to anoxemia There was marked edema of the entire brain and dilatation of the meningeal and cortical venules These investigators have advanced the idea that anoxemia may be the cause of most generalized convulsions in pertussis In treating convulsions they found that agents aimed at overcoming anoxemia were more successful in reducing the mortality rate than was any other therapy The mortality rate in patients with pertussis treated by sedatives lumbar puncture etc was 78 per cent but in patients treated in addition with early transfusions of whole blood the mortality rate was 35 per cent

Patients with convulsions are benefited by an oxygen tent blood transfusions lyophilic human serum or intravenous hypertonic sucrose solution in addition to the usual anticonvulsant drugs

The central nervous system complications deserve far more atten-

tensity, it lasts for a week or ten days During the third phase, although the frequency of the attacks may remain the same, the intensity diminishes increasingly until the frequency and intensity are both declining This third phase may last as long as two to five months but generally about four weeks The time comes when the paroxysms occur only at rare intervals sometimes as long as several days between attacks During this last stage however, the more severe paroxysms may recur at any time induced by such indiscretions as over-exercise, over eating or too much excitement

During the height of the disease there is often a characteristic puffy bloated appearance of the face edema of the eyelids and subconjunctival hemorrhage The lungs often develop marked emphysema and on auscultation are filled with moist, coarse rales Frequently there is a right-sided dilatation of the heart and the second pulmonic sound is more accentuated than normal The pressure in the lesser pulmonary circulation is increased which together with the marked hyperemic condition of the respiratory tract, accounts for the frequent hemorrhages which appear as streaks of blood on the coughed-up mucus

During severe complications the character of the cough often is modified or the whoop may be absent altogether during the acute period of a severe complication but returns after the worst stage of the complication has passed

In a certain number of cases especially during an epidemic there may be a number of mild atypical cases in which there are no typical whoops These cases may be recognized by the proxysmal cough which continues until the irritating mucus plug is dislodged There may be vomiting and the same suffusion of the face as in the typical cases

Complications

The most frequent complications are those due to mechanical causes Epistaxis occurs due to intense venous congestion Hemorrhages into the conjunctivae have been mentioned already as well as those from the bronchi More important still are intracranial hemorrhages which may occur during a severe paroxysm and can cause permanent damage A certain number of cases of epilepsy undoubtedly owe their origin to these intracranial hemorrhages In cases of profuse intracranial hemorrhage permanent spastic conditions and mental deterioration as well as coma followed by death may occur Other results from this most dreaded

previous history of chronic bronchitis following whooping cough These cases were sensitive to the bacterial proteins of the organism cultivated from the tracheal mucus

Otitis media may be mentioned as a frequent and painful complication of pertussis

The following table (Table I) dramatically points out the reason pertussis is a dreaded disease in the young infant

TABLE I

TOTAL DEATHS FROM PERTUSSIS BY AGE
UNITED STATES 1938–1940

UNITED STATES CENSUS BUREAU MORTALITY STATISTICS

Age	Number 3 year total	Per cent of total
Under 1 month	396	3 7
Under 2 months	1166	10 9
Under 3 months	1061	9 9
Under 4 months	791	7 4
Under 5 months	646	6 0
Under 6 months	515	4 8
Under 7 months	50	4 7
Under 8 months	458	4 3
Under 9 months	447	4
Under 10 months	417	3 9
Under 11 months	361	3 4
1 year	363	3 4
years	104	19 6
3 years	668	6
4 years	31	9
5 to 9 years	151	1 4
10 years and over	114	1 1
Total	10 730	

DIAGNOSIS[22, 32]

The diagnosis of whooping cough usually *is not difficult* except in the catarrhal stage Even when the whoop is absent the paroxysms in

tion than they have received in the past, although it is not true that all convulsions during whooping cough must lead to serious sequelae As a clinical fact in most instances where a convulsion occurs recovery is complete This is not true when the convulsive state is maintained

The most frequent of the serious complications are due to secondary infection of the respiratory tract Pneumonia causes the greatest mortality and renders whooping cough one of the most dreaded diseases of infancy and childhood Bronchopneumonia is the most frequent type although lobar pneumonia may occur in older children Either form appears during the paroxysmal stage, usually at the height or during the decline The whoop may disappear although the cough becomes more persistent and there is always increased malaise and a rise in temperature *In debilitated children the onset of pneumonia may be most rapid*, or the time of onset may be difficult to set The diagnosis of these complicating conditions does not differ from that of ordinary bronchopneumonia or lobar pneumonia

Some infants die from mechanical difficulty when a paroxysm overtakes them as they sleep Very young infants or debilitated children should be watched constantly for this reason In infants malnutrition becomes very pronounced in hot sections of the country, and in these areas diarrhea is a very serious complication Marasmus and atrophy with persistent gastrointestinal symptoms or chronic bronchitis produce the late mortality

During the course of the disease the *tracheobronchial lymph nodes* are involved and they may remain enlarged for months after recovery This condition is difficult to differentiate from a tuberculous infection of these nodes In children who have been exposed to tuberculosis and have a tuberculous infection of these nodes whooping cough often furnishes the direct impetus for initiating a general and often fatal tuberculosis By no means can we say that all cases of tracheobronchial adenitis end in such infection The area of infection in these cases undoubtedly becomes more extensive but it does not always develop into a disseminated tuberculous disease Such cases need careful and prolonged convalescent treatment in order to raise the resistance against tuberculosis or other acute infections

The chronic bronchitis which sometimes follows whooping cough offers an opportunity for sensitizing the patient to the secondary bacterial invaders such as staphylococci streptococci influenza bacilli or any of the other numerous organisms found in upper respiratory tract infections The writer has found a number of cases of asthma giving a

proved to be more satisfactory than the cough plate. A swab on a rather long thin wire is introduced through the nares to the nasopharynx or through the mouth to the nasopharynx and then is streaked on Bordet's medium and incubated at 37° C for 4 days.

Fleming showed that penicillin in suitable concentration inhibited secondary contaminants and allowed an almost pure culture of *H. pertussis* to grow on a Bordet medium. This led to a useful modification of the nasopharyngeal swab technic and was introduced by Bradford, Day and Berry in May, 1946. They take a postnasal pharyngeal swab, moisten it with a loopful of penicillin (1,000 Oxford U/ml) and streak it on Bordet's medium. They obtained 97.6 per cent positive cultures for all stages of the disease. A control group of cultures in which no penicillin was used on the medium gave 76.5 per cent positive.

The complement fixation and agglutination tests are other methods of diagnosis which will be described in detail under Prophylaxis. All of the tests described under Prophylaxis, which have been used to test immunity after injections, have been employed as methods of diagnosis.

Prognosis[24, 9]

The prognosis of whooping cough depends on the severity of the case. The uncomplicated typical pertussis case runs the usual course of symptoms and leaves the patient with no evidence of the disease aside from a possible weakness from the vomiting and the paroxysms. Complicated cases have a prognosis which is dependent upon the severity of the complication.

Whooping cough can result in mortality. A study of the mortality statistics shows that at very young ages whooping cough is more fatal than measles. Crum[9] gives the following interesting summary. In the whooping cough mortality 39.3 deaths in every 1,000 were at ages under one month, while in the measles mortality at the same ages there were 1.6 deaths among 1,000. Under the age of one year 554.7 out of every 1,000 deaths were from whooping cough, while 34.4 were from measles. In the registration area of the United States 95.4 per cent of all the deaths from whooping cough occurred at ages under five years as against 80.6 per cent for the same ages for measles.

Crum[9] also gives statistics from twenty-four countries which show that 1 per cent of the grand total of deaths from all causes were due to whooping cough. The countries represented included such widely sepa-

crease in intensity, unparalleled by general symptoms in sufficient number and this should be enough for a positive diagnosis. Such cases usually appear in epidemics which further renders the diagnosis comparatively easy to make.

A certain number of milder epidemics have been shown to be due to the parapertussis organism which produces a mild type of whooping cough. Eldering and Kendrick[30] reported an organism which resembled the *Hemophilus pertussis* and the *Bacillus bronchisepticus*, but which was shown to be neither of these and was designated as the *Bacillus parapertussis*. *B. parapertussis* often causes some difficulty in making a positive diagnosis of whooping cough. The only way to differentiate positively the *H. pertussis* and the *B. parapertussis* is by bacteriological and serological methods.

The chronic bronchitis which certain children are prone to have is a difficult condition to differentiate from whooping cough. The cough in these cases usually is staccato in type due to the enlarged tracheobronchial lymph nodes. However, the course of the disease and the appearance of the child are so suggestive that diagnosis seldom is difficult if observation over a long enough period is possible. The blood picture in these cases, i.e., the absence of lymphocytosis, is a great help.

An examination of the blood will show during the first stage of pertussis a definite leucocytosis with a constant increase in lymphocytes and a decrease in polymorphonuclear cells including the eosinophils. This picture will remain constant throughout an uncomplicated case. With the advent of secondary infections or complications the polymorphonuclear cells become increased.

The diagnosis in adults is more difficult owing to the fact that pertussis often is atypical, or that other types of bronchial irritation produce a somewhat similar cough. The facts that the disease appears in epidemics, and that children under five years are most susceptible to infection normally narrow the field of communicability and observation.

Whenever there is a doubt as to the diagnosis the laboratory is a useful adjunct in establishing the diagnosis of whooping cough. Cough plates are used frequently. A patient is made to cough on a blood potato-agar medium which then is incubated for 4 days and examined for typical colonies. The usefulness of the cough plate is limited somewhat by the fact that positive cultures generally are found only in the early stages of the disease.

In 1940 the nasopharyngeal swab was introduced and this method

proved to be more satisfactory than the cough plate A swab on a rather long thin wire is introduced through the nares to the nasopharynx or through the mouth to the nasopharynx and then is streaked on Bordet s medium and incubated at 37 C for 4 days

Fleming showed that penicillin in suitable concentration inhibited secondary contaminants and allowed an almost pure culture of *H pertussis* to grow on a Bordet medium This led to a useful modification of the nasopharyngeal swab technic and was introduced by Bradford Day and Berry in May 1946 They take a postnasal pharyngeal swab moisten it with a loopful of penicillin (1,000 Oxford U/ml) and streak it on Bordet s medium They obtained 97 6 per cent positive cultures for all stages of the disease A control group of cultures in which no penicillin was used on the medium gave 76 5 per cent positive

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chloroform may prevent convulsions Intubation also has been used in a few cases with considerable benefit

For internal use probably no drug has given more favorable results than antipyrin This can be given to infants in gr 1 (0 065 gm) doses every 2 or 3 hours children between 2 and 4 years may receive double this dose gr 2 (0 13 gm) Belladonna may be used for children two years or older beginning with a ¼ to ½ minim (0 015 to 0 03 cc) of the fluid extract every 3 or 4 hours Atropine may be used in place of belladonna starting with 1/1 000 of a grain (0 000065 gm) every 2 to 4 hours

It is a wise plan to alternate treatments because if one treatment is used for too long a period we fail to get sufficient response Antipyrin can be combined to advantage with sodium bromide although a sedative must never be given to children who are already lethargic or strangulation from the mucus plug may occur Antipyrin can be given also with cod liver oil with a purified product or with the vitamins themselves Whatever internal treatment is given care must be taken not to upset the digestive system

When nervous symptoms are prominent any of the sedative drugs such as codeine or chloral may be given for the purpose of diminishing the frequency and severity of the paroxysms It is a mistake to begin their use before the paroxysms become severe or to prolong their use beyond the period where they give definite therapeutic effect All of these drugs are used for symptomatic rather than curative effects

There are so many marked individual differences in drug toleration among the patients that it is impossible to be dogmatic about any specific drug Some drugs will work well on individuals at first and will be ineffective later Some patients will be benefited by a dose that would be insufficient for symptomatic relief in others In view of this condition only a general outline can be offered which must be adjusted to the individual response

Ormerod and Unkauf[1] obtained good results from large doses of vitamin C (cevitamic or ascorbic acid) 150 to 500 mgm daily were administered over a period of 8 days This medication resulted according to their findings in an immediate improvement of appetite marked reduction or arrest of vomiting reduction or disappearance of night cough as well as day cough and marked reduction in the frequency number and intensity of the paroxysms The duration of the cough was from 4 to 18 days with an average of slightly less than 1

An interesting fact is that Ormerod and Unkauf[1] started their study

rated areas as Japan England Chile and the United States The death rates varied in these countries from 66.5 per 100 000 population in Chile to 1.9 in Ceylon

Veeder gives the mortality in the United States according to age, as follows

Under 1 year	1 year	2 years	3 years	4 years	5-9 years
55.2%	23.5%	9.4%	4.6%	2.5%	3%

The highest mortality is during the month of August

In the United States the death rate among the colored race and the Filipinos is very much higher than among the whites, which also coincides with the percentage of cases recorded

Treatment[3, 13]

General Hygiene—General hygienic treatment is always of paramount value Fresh air and plenty of it, is a form of treatment always available Windy and dusty localities should be shunned as they are likely to produce paroxysms Very delicate children during the winter react better to fresh air indoors than to outdoor treatment, as outside exposure may convert a simple bronchitis into bronchopneumonia A change of locality may have a good effect Even a change of a few blocks in a city has given improvement The seashore or a sea voyage may decrease bronchial irritation and reduce the frequency of paroxysms of coughing due to the moisture and lack of dust in the air

Careful feeding especially in infants is essential Great care should be taken to regulate the food to avoid diarrhea or distention When vomiting is frequent smaller amounts of food should be given repeatedly and, if carefully administered may be successfully retained after a paroxysm

An abdominal binder may limit the number of paroxysms At least it will greatly reduce the frequently severe abdominal pain that accompanies a paroxysm

Medication—The number of drugs on the market as specifics for whooping cough is a sure indication that we have no specific Inhalations during the cartarrhal stage and often during the paroxysmal stage are of considerable value Creosote or any of the coal tar oil products may give relief They may be inhaled through a respirator or mask or vaporized and the steam inhaled In a few cases the administration of

Experiments with antibiotics show that they are of little or no value in combatting the original pertussis infection but that they may be of considerable value in the treatment of complications

Prophylaxis[11,63]

The value of preventive measures by the early use of properly prepared phase I *H pertussis* vaccine as a prophylactic measure has been demonstrated amply since Sauer's[66] first published work There can be little doubt of its effectiveness in the mind of anyone who has followed or taken part in the dramatic reduction of the morbidity rate due to the extensive immunization program carried on during recent years The only reports that have questioned the value of prevention by immunization have been proved to be the result of using improperly prepared vaccine In the study made by Doull and associates[4] in Cleveland the vaccine was washed with distilled water which has been shown by later studies to impair the antigen Other series that are quoted frequently are those of Goldberger and Siegel[19] and of McFarland and associates[6] where the vaccine was grown on a horse blood medium this has been shown to cause a rapid loss in the antigenic properties of phase I *H pertussis*

Omitting such reported failures there is an abundance of material concerning successful immunization programs Through the municipal government of Evanston Illinois and with the cooperation of private physicians from 1938 to 1945 Sauer[6] was able to immunize practically the entire newborn population annually which resulted in the situation that no child immunized in Evanston has developed whooping cough In this brilliant study vaccine was begun as early as the first month of life

Sako and associates[61] have reported a series in New Orleans where immunization was started in 4 000 infants less than 3 months old reducing the incidence of whooping cough in this group to 19 per cent as contrasted with 9 per cent in the exposed control group and showing a good immune response to early immunization

Waddell and Engle[69] also have had good results with early immunization programs and as seen by the mortality rate statistics protection during the first few months of life is of extreme importance Ordinarily the accepted age for beginning immunization has been the second half of the first year of life

with vitamin C after reports by Woringer and Sala[13(a)] reported scurvy in 4 pertussis cases. Ormerod and Unkauf[1] began this study on the premise that vitamin C is an essential part of the defense of the body against *H. pertussis*, and that this infection so depleted the vitamin supply of the body that scurvy resulted.

Vaccine.—During the last seven or eight years treatment with *H. pertussis* vaccine has come into general use. There is a general feeling that early treatment and large dosage of vaccine result in a milder case of shorter duration.

The type of vaccine that has been used most successfully is that known as phase I *Hemophilus pertussis* vaccine which is grown on human (placental) blood or sheep blood. A later development gives promise that *H. pertussis* organisms grown for several generations in a liquid medium may result in a more rapid growth of the virulent, antigenic form of the organism and minimize the chance of reactions.

The vaccines used most commonly at the present time are (1) aluminum-hydroxide absorbed vaccine containing forty thousand million organisms per c.c., (2) alum precipitated pertussis vaccine and (3) plain vaccine. The initial dose for children under one year should be 250 million organisms the first day, 500 million on the third day and the doses doubled thereafter every other day. The dose can be increased to as high as ten thousand million. Children over one year start with an initial dose of five hundred million, subsequent doses being doubled. The initial dose for adults is one billion.

Sera.—McGuinness and associates[33] recommended the use of hyperimmune serum developed from donors who had each received an initial course of four weekly injections of standard vaccine. About one month after the initial dose of vaccine the donor's serum is titrated. If the agglutination titer is 1:2560 or higher the donor is bled for serum. At each monthly bleeding the donor is given 2 c.c. of vaccine to maintain his titer. Patients who are in either the catarrhal or paroxysmal stage, were given three 20 c.c. injections of serum at 48 hour intervals regardless of age, making a total of 60 c.c. In many instances a fourth dose of 20 c.c. was given 5 to 7 days after the third dose to prevent a relapse. In some seriously ill cases several intravenous doses of from 50 to 100 c.c. of serum may be necessary, especially in the presence of bronchopneumonia. Most of the cases were given the serum intramuscularly but the intravenous route is preferred for the seriously ill. The results indicated that the serum was of considerable value in the treatment of the disease.

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Prophylaxis[41-69]

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The reason, ordinarily, for immunizing during the second half of the first year is because at this age period more lasting immunity is produced. However, as shown by Sako[61], whenever whooping cough is prevalent it would be advisable to start earlier, recognizing that the immunization must be repeated in the latter half of the first year.

When immunization has been given during the first four months of life, it should be followed by a booster dose during the latter part of the first year. It is generally agreed that in large population centers the eradication, or at least the control of whooping cough to the public health ideal (wherein the disease is kept at a rate lower than the usual expectancy rate) can be accomplished satisfactorily only if at least 80 per cent of the susceptible population has been immunized. This should be supplemented by the widespread use of booster doses during the second year and before the child enters either nursery school, kindergarten or the first grade. Many private physicians have been using booster doses yearly until the child enters school. In areas where a procedure of this sort has been carried out, the morbidity and mortality rates have been lowered appreciably.

Type of Vaccine and Dosage.—Phase I *Hemophilus pertussis* vaccine is commonly given with 3 doses of 80 to 130 billion organisms total divided into ½ c c or 1 c c the first dose, 1[illegible] to [illegible] c c second dose and [illegible] to 3 c c for the final dose, with a three week interval between injections.

The immunization program in Boston, conducted by a well baby clinic by Cravitz and Cauley[4], comparing Sauer's phase I *H. pertussis* vaccine with Lederle's detoxified pertussis antigen, showed that Sauer's vaccine was superior. Only 9.[illegible] per cent of the exposed children, who had been immunized with Sauer's vaccine, developed whooping cough as against 57.6 per cent given Lederle's antigen and 82.87 per cent of the non-immunized exposed children. The results indicate that the Sauer vaccine will afford excellent protection for at least 1 to 2 years. The detoxified pertussis antigen also is considerably less effective in modifying the course of the disease than is Sauer's bacterial vaccine.

During the last few years pertussis vaccine has been used in combination with diphtheria toxoid. The first injection of D P (diphtheria toxoid-pertussis vaccine) usually is given some time during the latter half of the first year, say at age of 7 or 8 months. One month later pertussis vaccine is given alone, the third injection consisting of D P is given alone at the end of the following second or third month. Another combination introduces diphtheria toxoid, tetanus toxoid and pertussis

vaccine The time intervals for this combination are the same as for the first named one Booster injections combined are then given yearly

Immunity Tests—The level of immunity can be tested by several different methods as follows

Agglutination test The following method of testing immunity is satisfactory A single drop of suitably prepared antigen stained blue and a single drop of the blood of the patient obtained from the finger as for blood counts are mixed on a ½ inch (1 3 cm) circle on a piece of white glazed cardboard the size of a microscope slide and tilted back and forth for one minute at which time the agglutination or clumping can be noted A negative reaction will show no clumping Agglutination tests should be given from one to two months after treatment with the vaccine as the agglutination reaction does not reach its height until then This method has the advantage of requiring only a small amount of equipment and of being done very rapidly

Many tests such as the complement fixation test opsono-cytophagic reaction test mouse protection test and various skin tests have been devised in attempts to measure immunity in individuals who have received prophylactic immunization However individuals vary so much in the production of immune bodies that no single test has been devised to show the degree of immunity with sufficient accuracy to be adopted as conclusive evidence of the efficacy of immunization programs The evidence of the level of protection at any given time is also inconclusive

Reactions to Prophylactic Measures—The severity of reaction depends so much on the individual at the time of injection that it is difficult to predict individual reactions Local reactions and sterile abscesses however can be reduced to a minimum with proper technique Every one giving injections regularly develops his own technique which usually is satisfactory to him and to his patient There are certain points however that are generally considered essential to good technique The injection should not be given superficially into the subcutaneous tissue and the needle should be dry The site usually chosen is the upper arm laterally and distally to the deltoid muscle After proper sterilization of the area the needle should be inserted deeply subcutaneously If a short interval after completing the emptying of the syringe is allowed the needle usually can be withdrawn free from a drop of vaccine which might cause increased irritation or even a sterile abscess With these simple precautions sterile abscesses usually can be obviated

The number of vaccine reactions has varied considerably in the writer's experience There have been fewer with the plain or with the

aluminum-hydroxide adsorbed vaccine Occasionally a sterile abscess may develop which, if left alone, usually will be absorbed gradually, if opened it can be treated in sterile fashion, applying either sulfa or penicillin ointment to prevent the development of any localized infection The reactions to any injection occur as a local swelling within the first 24 hours in most instances and can be treated successfully by local hot applications epsom salt compresses or a compress of equal parts glycerine and alcohol Systemic reactions if they accur at all from an injection, will appear within 12 to 24 hours and seldom last more than 12 to 24 hours after development In the writer's experience allergic children are more likely to develop reactions, either general or local than are non-allergic children Reactions may occur with every injection or with only one of the set

Social Aspects

Almost 60 per cent of infections can be traced to direct infection from neighborhood children another 10 per cent each to relatives and playmates, crowded cars movies and children s parties make up a large part of the remaining avenues of infection Carriers have been demonstrated and play a greater part in the beginnings of epidemics than is realized Luttinger[11] gives an interesting history of a carrier he designates as Pertussis Pete who successfully spread pertussis among his relatives in Harlem and Brooklyn to the extent of four families

The following Public Health circular, issued by the Board of Health of Provincetown Massachusetts vividly sets forth the public health preventive measures in a series of whooping cough Don'ts

DON'T SPREAD—the disease Prevent it by isolating the patient

DON'T FORGET—that the patient is a source of infection until the spasmodic cough is over

DON T FORGET—that an incubation period of 16 days must elapse before symptoms of the cough may be considerd as having passed

DON T FORGET—that the patients may continue to spread infection for six weeks after apparent recovery

DON T FORGET—that whooping cough should be reported

DON'T FORGET—that isolation need not include strict confinement to a room

DON T FORGET—that patients do better out of doors but must avoid contact with other persons

DON'T FORGET—that patients must not go to school theater church public assemblies nor ride in street cars or public conveyances

DON'T FORGET—that children when out of doors should be accompanied by intelligent caretakers as a protection to others

DON'T FORGET—that the safest course is to avoid infection

DON'T FAIL—to suggest that children with whooping cough who are given their liberty should be plainly labelled with a red cross or a yellow flag conspicuously displayed on their clothing to warn others

DON'T FORGET—that children under five require the greatest protection and care

DON'T FORGET—to seek medical advice

DON'T ALLOW—dogs cats or other domestic animals to be about the patient

DON'T FORGET—that the control of whooping cough is in the hands of the public itself

DON'T FORGET—to impress the public of the dangerous nature of this infection

DON'T FORGET—that the disease is contagious both before and after the whoop

DON'T FORGET—that mild cases of the disease without the characteristic whoop spread the disease

DON'T OVERLOOK—the fact that whooping cough may infect adults as well as children

DON'T FORGET—to notify all friends of the family that your child has whooping cough

DON'T ALLOW—the nurse or whoever is in charge of the child to mingle with other children or to go near any children in any home park or public place

DON'T FORGET—that if the child is by accident in the company of other children and has a coughing spell to cover the mouth and nose with a paper napkin and burn or wash this as soon as possible

DON'T FORGET—to do to other mothers children as you would have those children s mothers do unto yours

The health education programs which have been carried on so successfully by many Boards of Health national state and local have demonstrated the utility of community recognition of the necessity for intelligent handling of pertussis Careful quarantine measures should be carried out and community cooperation is necessary for strict reporting of the disease This of course requires early medical attention for ac

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curate diagnosis Quarantine during the early period of the disease should be strict Persons intimately exposed should be restricted as well as the patient, and immunization should be offered to the exposed members of the family

There is no doubt that whooping cough can be and should be eliminated from all communities It is gratifying to see the increasing number of communities which through their active and intelligent public health programs have achieved almost complete eradication of whooping cough

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CHAPTER XXVII

INFLUENZA

By HENRY A CHRISTIAN

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Definition—Influenza is an acute infectious disease usually of short duration and self limited caused by a virus which primarily injures the epithelium of the respiratory tract and which secondarily in many individuals extends to adjacent structures with the production of pulmonary lesions causing among its chief disturbances prostration fever severe aching in back and extremities conjunctival infection and very often bronchitis and bronchopneumonia The disease occurs in sporadic epidemic and pandemic forms the latter fortunately at long intervals Spread of the disease seems to be by patient to patient contact through a respiratory droplet mechanism

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History

The first recorded pandemic seems to have been the European one of 1510 Others that are recorded were in 1580, 1729-32, 1780-82, 1830-33, 1836-37, 1847-48, 1889-92 and 1918-20 The available descriptions indicate that the disease as we knew it in 1918-20, was repeated in the prior dates just given Means of recognizing the virus cause of influenza became available only after the 1918-20 pandemic, so it can only be surmised from clinical descriptions later supported by studies of the pathology that these pandemics were diseases very possibly identical etiologically with sporadic and epidemic cases of recent years whose virus etiology has been demonstrated That they were the identical disease in pandemic spread however does seem highly probable

Etiology

There has been much discussion as to the cause of influenza In the epidemic of 1889-1893 Pfeiffer[1] described a very small bacillus as the cause of the disease and this was accepted quite generally up to the occurrence of the 1918 pandemic Studies in this epidemic showed that the *Hemophilus (Bacillus) influenzæ* could be isolated from many patients with influenza often very early in the disease but also that numerous people who did not have influenza, harbored these same organisms There gradually developed increasing doubt that *Hemophilus influenzæ* caused influenza and the view that influenza was caused by a filter passing organism a virus increasingly was held This state of affairs continued until 1933 when Smith Andrewes and Laidlaw[3] succeeded in isolating a filtrable virus from patients with influenza by inoculating ferrets intranasally with filtrates of throat washings from patients with influenza Since then it has been believed very generally that influenza is caused by a virus and that bacteria are secondary invaders or possibly symbionts influenza then being a symbiotic infection comparable to swine influenza In the patients in the period, since the identification of a causative virus has been made *Hemophilus influenzæ* has not been found with any such frequency as during the pandemic of 1918-20 This has suggested to some that the pandemic form may have a symbiotic etiology virus and bacteria and this explains its much greater mortality Certainly in the 1918-20 pandemic there was a high incidence of the presence of bacteria notably *Hemophilus influenzæ*, *Streptococcus*

hemolyticus Pneumococcus and *Staphylococcus pyogenes aureus* For these reasons it seems desirable to retain for the present a description of these bacteria in relation to the pandemic of 1918 o and particularly of *Hemophilus influenzæ*

Pfeiffer s bacillus or *Hemophilus (Bacillus) influenzæ* is a small short bacillus decolorizing with Gram s stain growing on culture media in the presence of hemoglobin and particularly well in the neighborhood of other bacteria often it grows very sparsely Usually its colonies are very small and translucent readily overlooked on culture media except by experienced bacteriologists These facts as to its morphology and cultural peculiarities seem to have caused it easily to be overlooked or not got to grow on culture media and consequently there has been much variation in the percentage of occurrence as reported by various observers in different groups of cases The difficulties in maintaining its growth and of obtaining growth in different media have retarded studies of the biology of the organism Its small size its gram decolorizing property and its hemoglobinophilia have for most rested as satisfactory criteria of identification However such studies as have been made point to there being a very considerable group of organisms possessing these criteria knowledge of which is needed before one can determine the role of any particular organism in the etiology of influenza

The 1918 pandemic aroused widespread interest in determining its cause and many studies of the *H influenzæ* were made From these it is evident that a small gram decolorizing hemoglobinophilic bacillus corresponding to the organism described by Pfeiffer is present in the secretions from the respiratory mucous membranes in a very considerable proportion of the cases of influenza Keegan found it in 8 per cent Averill Young and Griffiths[3] in 75 per cent Rapoport[4] in 80 per cent and Stillman and Pritchett in 93 per cent others failed to find the *H influenzæ* so frequently The percentage found varies greatly in the hands of different observers from almost every case to a small per cent and it is not possible to say how far this variation resulted from failure to find the organism how far because of its absence in the patients at the time of the observation It is certain however that when carefully searched for by adequate technique this organism was found in a very large percentage of the patients of the 1918 o pandemic often early in the disease and sometimes in pure culture in fatal cases dying very early in the disease It is also true that the same technical skill applied in the study of normal controls both during and apart from periods when the disease was epidemic has shown that the same organism i e the same as

far as we can judge from such data as are given, is present very frequently in the respiratory mucous membranes of normal individuals, although less often than in the sick. Stillman and Pritchett, for example found 43 per cent. of normals harboring *H. influenzæ* in contrast to 93 per cent. of those having the disease. In other words, during this pandemic an organism, normally found in many people, merely increased in frequency of occurrence.

A more minute study of these hemoglobinophilic bacilli has shown their wide distribution and the occurrence of numerous strains as determined by cultural characteristics and especially by immunity reactions in animals[6], suggesting that we are dealing with a widely distributed family with many members. This multiplicity of strains has existed whether the organsims were isolated from normal controls, from acute cases early in the disease or even from fatal cases dying in a few days after onset. The variation in strains within an epidemic group has been taken by many as strong evidence against this organism being the prime cause of the disease (Park[6] among others) and it is very difficult to explain how a disease so explosive in its spread could be due solely to an organism with so many different immunity strains and suggests that the *H. influenzæ* is a secondary invader, possibly of such significance in the production of the lesion possibly as some think a symbiont in other words a normal inhabitant of the individual has acquired pathogenic properties as a result of some other unknown organism instigating the lesions. If the *H. influenzæ* is the cause of influenza, in its rapid spread from individual to individual it should enhance its pathogenicity but not vary its immunity reactions in kind, judging by what we know of other epidemic diseases of bacterial origin. We know that acute diseased conditions may result from organisms, which are normal inhabitants of the body, e.g. pneumococci and streptococci and that bacteria causing epidemics of disease, such as dysentery, are of different strains but with these in a given epidemic spread there are only slight variations in the immunity reactions of the recovered bacteria. However, we are not justified in excluding the *H. influenzæ* entirely from the role of etiology of pandemic influenza because of its wide distribution in normals and its variability in immunity reactions. Certanly we are dealing with a disease which has an extreme variability from a mild, not very contagious, endemic one to one of explosive violence, highly contagious and pandemic in its spread and with these differences it is not improbable that there might go concomitant differences in the etiological cause.

All efforts to produce the disease in man by using cultures of the *H.*

influenzæ introduced in various ways have failed[7] This organism is of very low pathogenicity for laboratory animals and animal inoculations have not thrown much light on the subject, except those of Blake and Cecil[8] who by intratracheal injection into monkeys of an *H influenzæ* greatly enhanced in pathogenicity by animal passage have produced an inflammatory change in the respiratory mucous membranes and a bronchopneumonia This latter evidence however may be taken equally well as merely indicative of the importance of the *H influenzæ* as a secondary invader causing complicating lesions By introducing these same organisms into the nose of monkeys they produced prostration fever rhinitis and tracheobronchitis which they consider like influenza in man These experiments are highly suggestive that *H influenzæ* may play an important role in the etiology of influenza but do not prove that it is the prime etiological factor

In addition to *H influenzæ* other bacteria frequently are present in patients with influenza this is particularly true when the lungs show pneumonic areas In this relationship the pneumococcus the staphylococcus and the streptococcus are very frequent other pathogenic bacteria occur infrequently These bacteria have the same cultural and immunological characteristics when isolated from patients with influenza as when isolated from other diseases Many observers believe that these several bacteria cause the pneumonia which is such a serious factor clinically in influenza being present almost constantly in fatal cases They are regarded by most observers as secondary invaders causing a frequent and serious complication of influenza pneumonia Whatever their relationship they are of importance clinically in suggesting the need for using chemotherapy in treatment as will be discussed on a later page under Treatment

Stimulated by the findings in 1933 of Smith Andrewes and Laidlaw[4] many investigations have been made to throw further light on the virus etiology of influenza Notwithstanding difficulties of experiment progress has been made and in 1940 almost simultaneously Magill[9,32] and Francis[30,31] discovered a second virus now known as influenza B virus the one discovered in 1933 by Smith Andrewes and Laidlaw now being called influenza A virus Furthermore negative results in the effort to identify virus A and virus B in some patients with influenza indicate the presence of a possible third variety of influenza virus differing from both A and B[34,8] Horsfall and his associates[35] found in a study of 850 cases of influenza approximately 30 per cent seemingly caused by this third variety There is as yet no definite determination of the pres

far as we can judge from such data as are given, is present very frequently in the respiratory mucous membranes of normal individuals, although less often than in the sick Stillman and Pritchett, for example, found 43 per cent of normals harboring *H influenzæ* in contrast to 93 per cent of those having the disease In other words, during this pandemic an organism, normally found in many people, merely increased in frequency of occurrence

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method of experimental contact of the well with the sick.[7,11] This is most surprising in view of its great natural contagiousness in epidemics. It suggests that contagiousness is at its maximum during the period of incubation and that the causative organism has very little resistance and is present in infective form only during the period of incubation or during that early period of the disease when the individual is but slightly sick.

Immunity

Influenza causes an immunity of short duration, possibly only a few months, possibly considerably longer, but with much variation of duration in individual cases. Some individuals have seemed protected completely against infection, at least in all outbreaks, both epidemic and pandemic; some individuals with apparently identical exposure fail to come down with influenza. Children on the whole have seemed more susceptible than adults. Infection with type A virus experimentally does not protect against type B virus, and there seem to be variations in the protective ability of different strains of the same virus. Immunity brought about by both active and passive immunization seems to be both humoral and local, since antibodies can be demonstrated in both the blood and the nasal secretions. It seems that antibody level in the nasal secretions is a better index of protection than antibody level in the blood. These various factors in immunity are of basic importance in the problem of prophylaxis against influenza and how best to attain and maintain it.

Epidemiology

Influenza appears to be the only remaining one of the great plagues of earlier times. The disease which was the cause of some other past plagues remains, but in modern times in civilized communities such diseases except influenza no longer sweep along carrying disability and death to a large proportion of the community. Periodically influenza has swept along, pandemic in character, attacking a large proportion of the people of the world, causing a very heavy toll in deaths. It seems clear that influenza smoulders in a community with sporadic cases and occasional local epidemics. It has been suggested that there is an endemic focus, possibly in Turkestan, from which pandemics start.[4] Then sud-

ence of a third variety of influenza virus However, failure by competent observers to demonstrate virus by methods that do demonstrate the presence of virus A or virus B in throat washings from patients with clinical influenza and the absence from the blood serum of these patients of antibodies of virus A or virus B do suggest strongly that there is a type of influenza or some disease very closely related to influenza which is caused by a virus or viruses other than influenza virus A or B There is the possibility that with more transfers of the disease to animals and the use of neutralization tests and tests for specific antibodies, not a third virus but several additional viruses will be found However, it seems justifiable at the present time to say that influenza is caused by organisms of the virus group not by a single virus but at least three, possibly more than three varieties or types of virus

The virus of influenza is pathogenic for hamsters and Swiss mice The virus can be cultivated easily in the allantoic fluid of the chick embryo From the latter growths vaccines can be prepared in large quantity by appropriate methods These viruses cause in man with influenza demonstrable increase in specific antibodies as do vaccines made from them All of these methods have been applied in the study of recent epidemics and have thrown much light on the epidemiology and clinical characteristics of influenza

The studies of virus in influenza have been made on groups of patients constituting slight to fairly extensive epidemics There has been no opportunity to study a pandemic by the newer methods of investigating viruses since none has occurred since that of 1918-20 So it is possible that the virus of pandemic influenza still is unknown Clinically influenza apart from its occurrence in pandemics is not a disease sufficiently characteristic to justify saying that the patients, in whom these virus investigations have been made have had with certainty the same clinical disease Furthermore uncertainty arises too by reason of the recognition of a considerable group of diseases with bronchitis and pneumonitis (pneumonia) apparently of various causes including rickettsial causes clinically not the same as what we have called influenza this increases the difficulty of definite and certain diagnosis Even in a single outbreak of influenza often there is evidence that more than one variety of influenza virus has been causative It may be that with influenza and virus a situation analogous to pneumonia and pneumococcus exists and that we deal us with the pneumococcus with types rather than varieties of virus organisms

All attempts so far have failed to reproduce influenza in man by any

The history of these recurrences is full of interest an entertaining account is to be found in the Annals of Influenza[11] published by the New Sydenham Society in 1852 In it these outbreaks are traced to the XVI century

A pandemic once begun the disease has always been repeated several times as epidemics at intervals of six to twelve months so that a given locality may anticipate a second outbreak the next year and very probably a third one but with a decline in severity with repetition Moreover the main outbreak is often preceded by a milder one this apparently was true of the 1918-20 pandemic at least so far as the United States was affected

Influenza seems to be a contact infection with an incubation period of about two days Spread probably is by droplets from the respiration tract of the influenza patient to the respiratory tract of well individuals This was worked out to be the case in some country communities rather sparsely settled in which contacts and onset of disease could be traced and in special instances in which time of a single exposure was accurately known[5 10] The two day incubation period seems very definite The attempt in the pandemic of 1918 20 to produce influenza in susceptible humans however by various forms of contact and by spraying of nasal secretions etc has failed to produce the disease [11] In this case the contacts were made with individuals having active influenza and by using material for spraying etc obtained from those in whom the disease had developed This suggests that the contagiousness had largely been lost at this time Our own observations at the Peter Bent Brigham Hospital suggested that nurses and orderlies acquired the disease not from contact with influenza patients in the hospital but from each other or from outsiders indicating that possibly the contagiousness is in the early periods of the disease not unlikely during the two days of incubation The facts remain that influenza is a disease which very evidently spreads with great rapidity in a community and which can be kept out by complete isolation as shown by certain quarantines such as were maintained on easily isolated islands and in certain institutions that it is a disease in which there is no evidence of an intermediate host but much evidence of contact spread and yet it was not produced deliberately in man by a large variety of means tried for transmission This would seem to indicate a very high contagiousness at a very early period with a rapid decline or complete disappearance of contagiousness by the time the symptoms have developed

Epidemiological studies of the 1918 20 epidemic show that an out

denly for some unknown reason the disease has changed its character become highly contagious increased in virulence and spread over communities countries and continents until it girdles the globe as did the 1918-20 pandemic The pandemic gradually burns itself out to be followed by several recurring epidemics during the succeeding two or three years until it again becomes quiescent, although sporadic cases remain

Why it should so behave we know not Is it that a more suitable soil for it arises This hardly seems the sole reason, even if it is an important factor Changed soil hardly explains its sudden appearance and wide distribution Is it the result of an enhanced virulence of the virus This theory seems more in accord with the facts, but we have no positive proof Once started it is probable that rapid passage from individual to individual increases virulence and that the epidemic subsides because only the more resistant and completely resistant remain for possible infection Some observations[33] on poliomyelitis, however, show that experimental passage of the virus through susceptible animals enhances virulence for a time then this degree of virulence is long maintained finally it decreases although the virus still is being passed from susceptible animal to susceptible animal in the same way and with the same time relations so that it may not be merely a question of suitable soil having been exhausted Similar observations have been made on bacterial infections natural in mice Another possible cause for the rapid increase in severity with the greatly enhanced mortality which occurs during pandemics may lie in a change in resistance to secondary invaders, chiefly bacteria In the pandemic of 1918-20, when it reached its greatest severity death almost always resulted from secondary streptococcic or other bacterial pneumonia Before the complicating pneumonia became very frequent mortality remained low, at that time there were many cases but few deaths

Once started on its pandemic course influenza spreads with great rapidity, apparently by contact as fast as existing means of communication make possible Soon it has passed from country to country until so far as we know all nations and peoples have suffered In the occurrence of pandemics there is a rough periodicity of twenty to thirty years complicated somewhat by epidemics in between, which although of wide extent, are not pandemic in character Furthermore, in earlier days communication was slower and news as well as disease spread gradually, hence it is harder to recognize pandemics from extensive epidemics, and the periodicity is not so certain as in more recent times

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break actually occupies a considerable period, five to eight or more weeks although during a period of eight to ten days the number of cases increases very rapidly to a peak, which is maintained for two to three days and then the peak is followed by a rapid decline for eight to ten days, after which the curve falls slowly so that for some time a moderate number of cases occurs This curve actually varies much in different localities and sometimes instead of one there are several peaks Careful study shows that the real outbreak is preceded for some time by a moderate occurrence of cases and probably antedated by a moderate epidemic, often not recognized as such which comes several months before the explosive outbreak In other words the explosive character and unheralded epidemic are not really such, the actual beginnings and warning signs instead have not been recognized by a community and physicians the majority of whom have not experienced a similar pandemic and so are not trained to recognize the early beginnings It seems very certain that influenza existed in many parts of the United States in the winter and spring prior to the October, 1918 intense outbreak

It is difficult to say what per cent of the population are attacked in an epidemic Estimates for different epidemics and for different localities in a given epidemic vary very greatly depending on contagiousness, opportunities for contact season of the year etc In training camps in this country where young men in good health were in quite close contact, the percentage of infection varied from 49 8 per cent in Camp Cody to 9 7 per cent in Camp Lewis[16] It has been estimated that in the 1918 epidemic in the United States influenza caused approximately 550 000 deaths[17] but there are no very accurate figures on which to base an estimate of the number of individuals who had the disease Influenza was not a reportable disease in the earlier parts of the epidemic even in places where vital statistics are quite accurately made up and for much of the country no reports of incidence were made However, if we assume a mortality of one per cent which is probably somewhat too little there were fifty-five million cases or about half the population, if the mortality was two per cent, the number of cases in the United States was half this number or one-quarter of the populaton which would seem nearer in accord with personal observations and the fact that in 1918-20 older people very largely escaped Anyhow, in the United States as elsewhere the number having the disease is appalling and influenza is truly a calamity to the world when it assumes pandemic proportions

Between pandemics there occur outbreaks of lesser spread in contrast to pandemic influenza this form now is known as *epidemic influenza* Such outbreaks occur at intervals of one to six years It is from patients with this type of epidemic influenza that viruses A and B have been isolated and causative of which there may be one or more so far unidentified viruses as already discussed in the section on Etiology Epidemic influenza caused by virus A and by virus B has shown somewhat different periodicity virus A influenza having a cyclic recurrence every two or three years virus B influenza a cyclic recurrence every four to six years Epidemic influenza is much less severe in general than pandemic influenza and has a lower attack rate but there is considerable variation in individual cases from a rather mild respiratory infection to a few severe fulminating cases reminiscent of those seen so frequently in the 1918 20 pandemic Still it seems reasonable to regard all of these forms as essentially one disease caused by closely related viruses as is pneumococcus pneumonia with its many immunologically types of pneumococci

Pathology and Pathogenesis

From a pathological viewpoint influenza is almost solely a disease of the respiratory tract In no fatal cases are lesions absent from this tract and in practically all there is a combination of tracheitis bronchitis and bronchopneumonia with the bronchopneumonia playing the leading role so far as microscopic changes are concerned The pathological changes caused by the virus of influenza are primarily in the ciliated epithelial cells of the respiratory tract from nose to bronchi with subsequent extension to the bronchioles and pulmonary parenchyma Probably the mucosa of different parts of the respiratory tract may be involved independently at different times or all at once Adams[4] found in swab preparations from the pharynx of patients during influenza A large sloughed off sheets of epithelial cells and an exudate of mononuclear cells In a case complicated by staphylococcal infection the mucous membrane from trachea to tertiary bronchi was covered with an exudate overlying an intensely congested surface and the epithelium of the trachea was completely destroyed[16] In experimental infection of animals there is necrobiosis desquamation and fibroid necrosis of the respiratory tract epithelium with denudation of the surfaces and inflammation in the submucosa lesions consistent with the changes just described in the epithelium from human cases of influenza

As in man fatal cases almost always show bacterial invasion, the resultant pathology is the result of the combined effects of the influenza virus and the bacterial invasion The resultant lesions are tracheitis bronchitis and bronchopneumonia The best opportunity for the study of the pathology of influenza in recent years was afforded by the many fatal cases in the pandemic of 1918-20, and the following description is based on these studies

The bronchopneumonia of pandemic influenza[16,18,19] presents a very varying picture which is as would be expected when we bear in mind two facts, namely, a varying bacterial flora acting pathogenically and a varying duration of disease with varying extent of involvement This accounts for the very different descriptions of the gross lesions that we see in the literature, for they were based on observations made in different localities in which different bacterial groups preponderated, and in which the disease was more or less quickly fatal However, when a number of descriptions are read or one's own material is arranged in rough series of similar lesions of varying duration it becomes clear that all represent gradations in an essentially similar process, influenced in its appearance by a more or less marked action of a given type of bacteria

In the earlier stages the lungs are engorged, moist bloody They are partially collapsed and dark red Their surfaces are mottled by subpleural extravissations of blood There is but little fibrin on the pleura The mucosa of bronchi and trachea is similarly dark red and moist There is no true consolidation as one expects in a pneumonic process and the picture is quite different from the usual types of bronchopneumonia The one most striking feature is the increased fluid exudation, blood tinged and thin The condition is essentially an inflammatory usually hemorrhagic, edema The cut surface is mottled in general bright red with irregular areas of darker red corresponding to hemorrhages and in places some grayish areas The lung is soggy and yields much fluid thin and blood tinged or actually bloody

In the later stages the lungs are more voluminous and more nodular Subpleural lymphatics are injected and often show as a very distinct tracery There is more fibrin on the pleura but as a rule not very much certainly not the shaggy layer so often seen in lobar pneumonia Bronchi and trachea are injected Very often the bronchi are dilated influenza has shown that an acute bronchiectasis is possible and may develop in a few days ten or twelve or even less Interstitial emphysema, too, is common When the pneumonic areas are large and have coalesced consolidation frequently involves an entire lobe but usually it is definitely

a confluent bronchopneumonia rather than a true lobar pneumonia although the latter does occur occasionally The lung is rather friable Its cut surface shows mottling with grayish areas against a background of congested lung Areas of hemorrhage are frequent even in these later stages Quite often there are areas of a more opaque appearance due to beginning necrosis A little later these soften, break down and form irregular abscesses or areas of gangrene

In both the early and later stages there is great irregularity in size and distribution of the areas of hemorrhage and consolidation Usually the lower lobes show more extensive involvement and from appearance are the location of the first lesions in the developing process The regularly scattered shotty areas of consolidation so often found in other bronchopneumonias in my experience as well as that of many others were infrequent and when found were apt to be in those dying rather late in the disease In this form often the bronchus in each area was filled with a yellowish tenacious plug of pus and the intervening lung tissue was rather distended with air I have seen this picture in a patient dying late in the disease apparently from sudden suffocation as if the filling of many terminal bronchi with tenacious exudate stopped an adequate respiratory exchange

Microscopically in the earlier stages capillaries are engorged and the alveoli are filled with serous or hemorrhagic exudate Polynuclear leukocytes are few the cells present are mononuclears, in part desquamated epithelial cells *in part mononuclear leukocytes* Fibrin is almost absent Later polynuclear leukocytes are present, and fibrin is found more often but it still *is sparse in contrast to other forms of pneumonic consolidation* Alveolar walls and other structures often show degeneration up to actual *necrosis There is evidently some toxic substance present* which early in the disease causes death and disintergration of cells Bronchi contain *the same sort of exudate as found in alveoli and their walls are at first* edematous and later show cellular infiltration more with mononuclear *than polynuclear cells Bronchial epithelium often is desquamated leav*ing a bare surface Interstitial emphysema often is found, the air making its way *along the peribronchial and perivascular connective tissue toward* the hilum of the lung thence to mediastinal and subcutaneous tissues

In many lungs there is found a curious hyaline material along the walls of distended alveoli and bronchioles This seems rather a unique feature of the influenzal lung and Wolbach[14] thinks it may be in a sense a specific or at least a pathognomonic lesion The material differs from

fibrin in microchemical reactions and seems to be some form of hyaline degeneration or deposition or a hyalinized fibrin

It would seem that resolution is rather slow but in many cases complete Peribronchial thickening, as revealed by the x-ray, often persists for a long time Organization is found often in those dying somewhat late in the pneumonic process and probably is present in many recovering cases These two processes explain persisting physical signs often met with, which suggest a possible tuberculosis in patients who have had influenza

As already mentioned, the pleura often shows fibrin, but actual clinical pleurisy is infrequent in the early part of an epidemic In the later stages of an epidemic empyema is more frequent Lymph nodes draining the lungs are swollen and congested

The heart is remarkably free from lesions other than the minor changes found in febrile diseases Occasional pericarditis and rare vegetative endocarditis are encountered in most autopsy series In the testes there is aspermia, and focal degenerations usually are found[18] The other viscera rarely show changes except the minor ones of an acute infection

Besides the lungs the other striking lesion of influenza is the frequent degenerative change found in the skeletal muscles Waxy degeneration of striated muscles is frequently seen, and there may be actual necrosis with disintegration and often hemorrhage The frequency with which these lesions are noted is remarkable, if thorough and complete examinations of the skeletal muscles could have been made, these lesions undoubtedly would have been found very often The changes are like those encountered in typhoid and are most often observed in the rectus abdominis and pectoral muscles Some call these changes Zenker s degeneration of the muscles

As complications extension to the mediastinum with mediastinitis was frequent as was pleurisy, often of a serous hemorrhagic rather than purlent type In some patients from rupture of air sacs mediastinal and subcutaneous emphysema developed It is interesting that the surfaces of these air sacs not infrequently showed a hyaline or fibrinoid lining as was seen in the pulmonary parenchyma itself Bronchiectasis and lung abscesses were found fairly often, both sometimes developing very acutely Acute sinusitis and mastoiditis were found as complications Encephalitis and meningoencephalitis were found infrequently Other complicating lesions of great variety such as pericarditis endocarditis, myocarditis, peritonitis, arthritis, nephritis occurred as might

be expected in a disease with so many other organisms, especially streptococci, present, but these did not occur with great frequency.

There is considerable evidence to be found in the study of the lungs of the earlier cases that the process is a descending one extending along the bronchi to the pulmonary tissue. Animal inoculations suggest, however, that there may be a widely spread, simultaneous involvement of the epithelium at different levels of the respiratory tract. Often it seems as if the extension took place through the walls of bronchioles to air-cells, centrally as well as along the lumens to the connecting air sacs.

The bacteriology of influenzal bronchopneumonia, as already indicated, does not seem to be a constant one. Bacteriological studies made at different places during the 1918–1919 pandemic showed that in one place one bacterium predominated and in another a different one with mixed infection by two or more being frequent. Various types of pneumococci, of streptococci, of staphylococci and of *Hemophilus influenzae* were found often in a given locality while other bacteria occurred much less frequently.

Clinical Course of Pandemic Influenza

In the 1918–1919 pandemic influenza presented essentially the same clinical picture as in previous outbreaks. Apart from the study of its bronchopneumonia, recent investigations have added almost no new knowledge of the clinical course of the disease. If one reads the accounts of earlier epidemics one is struck immediately with the fact that the descriptions given of the disease correspond very closely with one's own observations of patients in the 1918–1919 pandemic. This holds true of even the very early descriptions if allowance is made for the terminology of the time and the absence of certain instruments of observation. I have been greatly impressed that pandemic influenza in its recurrences has changed not at all in character. Of course different writers emphasize different features, but never is there any doubt but that they are all dealing with the same disease entity. Furthermore, epidemics vary in severity and frequency of complications and sequelae, but the basal picture remains the same. There is a very voluminous literature on the clinical aspects of influenza, especially with reference to the recent epidemic. The clinical account here given is based in the main on my own experience in the 1918–1919 outbreak.

Onset usually is sudden. Incubation period approximates forty-eight hours very closely. Sometimes there are prodromal symptoms

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Onset usually is sudden Incubation period approximates forty-eight hours very closely Sometimes there are prodromal symptoms

of a vague character: malaise, slight headache, fatigue. Oftenest the transition from health to sickness is abrupt. There are severe headache, backache, pain in the eyes, photophobia, pain in the muscles and bones, anorexia, nausea, vomiting, nose bleed, great mental and physical depression, chilliness, fever, coryza or cough, sometimes only a few of these, often many combined. These symptoms may appear with such suddenness that the business man, who starts to walk home, is compelled to sit on a doorstep until rescue comes, and he is transported to his bed. Prostration, chilliness, headache, backache and pain in the limbs are the most frequent in the grouping of onset symptoms. A sudden onset is most frequent, but in many cases there is a gradual appearance of symptoms, and in a few there is a curious intermittence in symptoms. There is nothing particularly characteristic of any single one of these symptoms.

Examination of the patient at the onset shows little but an obviously ill and uncomfortable patient with a temperature of 102° to 104°F. In the early days there is often a marked, cherry red erythema of the face and neck, frequently extending to the chest and arms. This also is evident in the mucous membrane of the mouth. Sometimes this arouses the suspicion of scarlet fever. Later in cases with pulmonary involvement, cyanosis replaces the erythema. In many cases no other signs develop, and after a duration of three to seven days the fever subsides and convalescence begins. The temperature varies moderately from observation to observation, in about half it falls abruptly to normal or subnormal (Charts I and II), and in about half it falls gradually (Chart III). In the majority of cases, however, there are evidences of some involvements of the respiratory tract: nose, pharynx, larynx and trachea. Tonsillitis is infrequent. Visible mucous membranes are congested, and there is an increased secretion. The patient has a stopped up nose, an uncomfortable raw throat or a distressing hacking cough. At some time during the course of the illness almost all patients have cough. In the early stages this is apt to be dry and racking and associated with substernal soreness or tenderness. Later sputum appears, at first tenacious and mucous, still later more profuse and mucopurulent, quite often blood streaked or bloody. In some of these cases with cough and sputum coarse ronchi or sibilant rales are heard. Many of these patients recover without other pulmonary signs, others develop bronchopneumonia.

Epistaxis often has been a notable feature, much more common than in typhoid. Sometimes it is an initial disturbance, at other times it occurs in the course of the disease. Usually blood loss is slight, but at times it is very considerable. Much more rarely are there gastric or intestinal

hemorrhages Hemoptysis is not infrequent Quite often patients menstruate in the early days of their infection out of relation to their regular time In all these bleedings the underlying cause seems to have been the intense hyperemia of the mucous membranes

Pulse rate is as a rule only slightly elevated (Charts II III IV, V VI) This is true even with high temperature or extensive pneumonia The pulse usually is between 80 and 90 and very rarely is it over 100 There is little evidence of any heart lesion and most autopsy reports give no cardiac lesions other than the slight microscopic changes of any febrile disease Respiration too is not increased except when there is extensive pulmonary involvement Blood pressure is normal or slightly subnormal The leukocyte count is normal more often subnormal so that leukopenia is quite characteristic and at times the leukopenia is marked ([illegible] 000 or less) Leukocytosis is slow to develop even with bronchopneumonia and is rarely marked counts above 15 000 to 20 000 being unusual even with pneumonia

Blood cultures are almost invariably negative The finding of *H influenzae* in the circulating blood is very rare Later when pneumonia develops blood cultures may show organisms pneumococcus streptococcus and staphylococcus most frequently The spleen probably is moderately enlarged in most severe cases but it is rarely palpable

Many of the severe cases show mental disturbances Very often they are very apathetic dull and expressionless they may be as if asleep with eyes half open but they respond intelligently to questions Very distressing are those cases which remain fully conscious up to the end I have seen them answer promptly that they felt quite comfortable and remain fully cognizant of their surrounding when their ashen cyanosis and cold sweat announced a speedy dissolution Other patients are in stuporous muttering condition comatose or actively delirious as the case may be Most patients with marked mental changes have a bronchopneumonia Following influenza a variety of psychoses may develop

Bronchopneumonia

By far the most serious condition in influenza is the pulmonary involvement bronchopneumonia by some considered a complication but occurring so frequently as to justify its inclusion as an integral part of the disease This was the cause of the high mortality and was present in practically every fatal case In a few patients bronchopneumonia seems

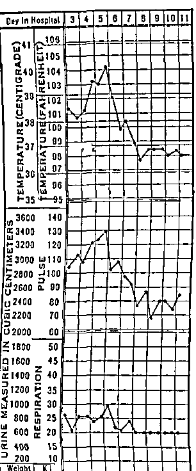


CHART I.—Uncomplicated influenza abrupt fall of temperature to normal.

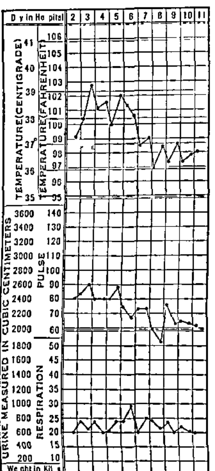


CHART II.—Uncomplicated influenza abrupt fall of temperature to slightly subnormal.

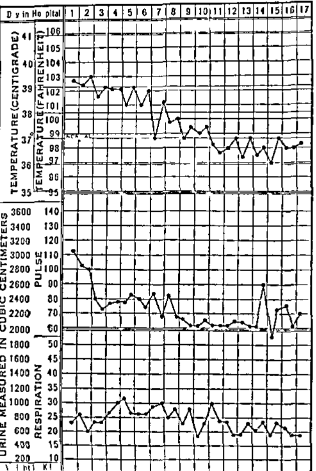


CHART III.—Uncomplicated influenza gradual fall of temperature.

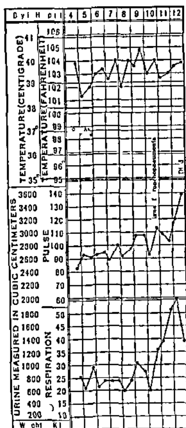


CHART IV —Influenza followed by bronchopneumonia On the day that physical signs of consolidation were made out and prior to this the temperature curve shows no change

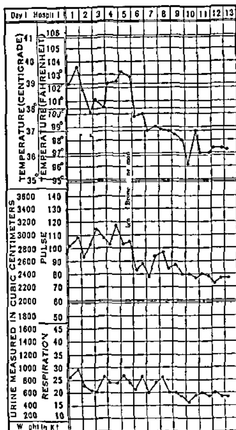
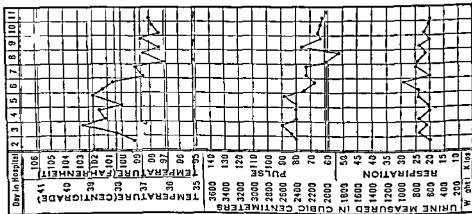


CHART V —Influenza followed by bronchopneumonia On the day prior to that on which abnormal pulmonary physical signs were made out the temperature rose and this rise probably represents the onset of bronchopneumonia

to develop almost at the outset of the sickness In others it appears in the early days but in most it begins from six to ten days after the onset Often in the group with early onset of bronchopneumonia and also in some with a later development the temperature chart (Chart IV) shows no indications of it usually in those with later onset, unless there was already a high fever present the development of bronchopneumonia is marked by a sharp or gradual rise in temperature (Chart V) with very moderate increase in pulse and respiration rate Very often the fever



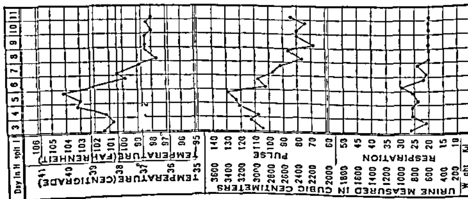


CHART I.—Uncomplicated influenza; abrupt fall of temperature

CHART II.—Uncomplicated influenza; abrupt fall of temperature to

CHART III.—Uncomplicated influenza; gradual fall of temperature.

of the primary disease has subsided and with a short interval of slight or no fever there is a secondary fever to mark the bronchopneumonia (Chart VI)

With the changes in temperature cough increases and there is more sputum Often the sputum becomes blood tinged or even bloody The prune juice sputum, so typical of lobar pneumonia, however is infrequent At the very first of the pneumonia there are no new physical signs or only scattered, medium sized rales Early, however in very many cases there appear fine, crepitant, frequently consonating rales over small areas Usually these are heard earliest in the back at the angle of the scapula oftenest at first on but one side These rales may be fleeting present at one examination but absent an hour later Their importance lies in the fact that they indicate a patch of consolidation even though there are no other physical signs to be made out with them Where they are heard x ray usually will show some increase in density and in early fatal cases there may be evidence indicating that here occurred the earliest focus of bronchopneumonia I myself most certainly did not appreciate how these few signs indicated consolidation until experience in the epidemic had shown me that this was the case

Often with these rales and usually by the next day other signs of consolidation appear Increased whispered voice transmission or a bronchial quality of the breath sounds most frequently accompanies the rales In some cases dullness on percussion can be made out over a small area Variation in these signs is a striking feature in the bronchopneumonia occurring in influenza so that at one examination dullness without other change is made out, and shortly afterwards either the dullness is accompanied by rales bronchophony or bronchial breathing or its has disappeared Sometimes such small areas are the sole evidence of pulmonary lesion in most cases the process extends and the area showing abnormal physical signs enlarges, or other areas appear until in some cases there are signs of very extensive involvement As a rule the lower lobes are most involved often the upper lobes show no signs of consolidation, or they appear only after they are quite marked in the lower lobes In fatal cases almost invariably the pneumonic process is much wider spread than definite physical signs have indicated

At the height of the epidemic many cases are seen with an early and very extensive pulmonary involvement In them physical signs may be confined to diffuse fine and medium sized rales and very slight impairment of resonance at the bases of the lungs behind It is this type of case

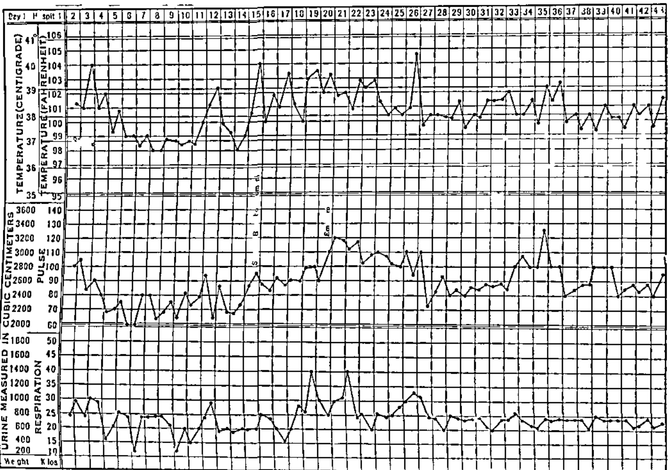


CHART VI — Influenza followed by bronchopneumonia The fever of influenza subsided but after an interval of several days the temperature again rose owing to bronchopneumonia Subsequently an empyema developed and was drained

is often extreme and the weakness and lack of energy persist for a long time even although there are no complications that have developed Possibly the long persisting muscular weakness can be explained by the lesions in the voluntary muscles already described If during the disease degeneration in them has been widespread it is reasonable to assume that recovery would be slow and muscle repair cause function disturbance for some time This condition is quite often regarded as an aftermath of neuritis it may be in many cases an aftermath of degenerative myositis

During convalescence bradycardia is not infrequent Ordinarily it is a simple bradycardia Occasionally the slow pulse results from heart block Extra systoles are common in convalescence and often persist to give the patients uncomfortable symptoms of apprehension palpitation and rarely anginoid pain These cardiac disturbances rarely are serious and they disappear with time

In early convalescence there is sometimes a vasomotor imbalance which causes the patient to faint when he attempts to get up In such cases examination both by ordinary means and by the electrocardiograph reveals no cardiovascular lesion and blood pressure is not low

Clinical Course of Epidemic Influenza

Epidemic influenza in contrast to pandemic influenza runs a much milder course possibly because secondary or complicating bacterial infection is far less frequent This is borne out by usually finding pneumococci streptococci or staphylococci present in the more severe cases and especially in the fatal ones Incubation period of epidemic, like that of pandemic influenza is from 1 to 3 days usually 3 days and onset as a rule is sudden with fever, chilly sensations prostration body aches headache and catarrhal symptoms referable to nose pharynx larynx or trachea one several or all Temperature rises rapidly usually to 10 to 104 F but in some to 106 F or even higher Pulse and respiration accelerate only moderately unless complicating bacterial pneumonia develops later on Early epistaxis is frequent Many patients become very listless Face neck and upper thorax usually is deeply flushed really an erythematous rash rarely with scattered petechial hemorrhages Similar erythema is present on visible mucosae of nose mouth and throat sometimes punctate sometimes diffuse sometimes with petechial hemorrhages Conjunctivae frequently are moderately injected and lachrymose A runny nose and soreness of the throat are common Cough often very

which shows a striking cyanosis out of all proportion to any dyspnea These cases are almost always fatal, and they live only a few days

Until the later stages of fatal cases pulse and respiration are, as a rule disproportionately slower than would be expected with the degree of fever present and very often the pulse remains relatively slow with a rising respiratory rate There is nothing characteristic of the fever curve It may be high and sustained or fluctuating, quite often fever is very slight even in some very severe or fatal cases In few diseases is the temperature, pulse and respiratory chart of so little value in indicating the patient s condition With beginning convalescence the temperature falls by crisis or by lysis, the latter being more common However I think a crisis is far more frequent than would be expected in broncho pneumonia

Cyanosis

Cyanosis has already been referred to Various explanations for it have been offered Pulse charts in these cases, as well as the quality of the pulse indicate that it does not result from cardiac lesions Respiration rate and absence of ordinary dyspnea suggest that its mechanism does not depend on any difficulty in getting air into and out of the lungs It has been suggested that it is due to vasomotor paralysis dilating the small vessels and so slowing the circulation, but this does not seem probable Methemoglobinemia is another explanation that has been offered, but the very sudden onset in many cases does not fit with this explanation The best explanation seems to be that it is an anoxemia due to the layer of fluid in the alveoli

The cyanosis in many of these cases is a very striking feature often spoken of as resembling that following gas poisoning of warfare The face is of a curious ashen gray color with bluish or purplish lips and a similar patch on the cheeks Trunk and limbs show much less of this than is found on face and neck although often the finger and toe tips are of a dull bluish color As already indicated, the cyanosis is often striking in a patient without subjective distress and air hunger, in other words a cyanosis without dyspnea With the cyanosis goes a cold, clammy skin and often one bathed in sweat These cyanotic patients rarely recover

Convalescence

Convalescence from influenza is as a rule, disproportionately slow in relation to the duration of the febrile period With the disease prostration

sidered as a complication It does not differ from lobar pneumonia complicating other acute diseases

Bronchiectasis appears to have followed previous epidemics of influenza as a chronic pulmonary condition with some slight frequency It is clinically similar to other types of bronchiectasis The rather frequent finding of *H influenzae* in the sputum in cases of chronic bronchiectasis[21] may indicate that the bronchiectasis developed as a sequence of influenza and that these bacteria had a pathogenic role or that the dilated bronchi of influenza furnished suitable conditions for the growth of an organism present as a normal inhabitant of the upper respiratory tract In the 1918 epidemic the quite frequent finding at autopsy of acute brochiectasis certainly proves a close relationship between influenza and bronchiectasis and suggests that in non fatal cases a similar acute bronchiectasis developed which gradually might change into a chronic bronchiectasis with very probably a quiescent intervening period so far as symptoms and physical signs are concerned Subsequently however this idea was not supported by any great frequency of postinfluenzal bronchiectasis

Pulmonary abscess and *gangrene* occur as rather rare complications of the later acute stages of bronchopneumonia Sometimes abscess occurs after convalescence from the influenza Multiple small abscesses are seen at autopsy and especially are they found when the staphylococcus pyogenes aureus is present in the pulmonary lesions

Pleurisy and Empyema —In the rapidly fatal cases the pleura shows but slight fibrin deposits With longer duration of the bronchopneumonia more fibrin is present Except in the very fulminant cases there is as a rule a moderate increase in pleural fluid Corresponding to these pathological findings clinical signs of pleurisy are few in the major portion of influenza patients even in those with extensive bronchopneumonia The sharp pleurisy pain so common in the beginning of lobar pneumonia is rare in influenza In the early stages of the pandemic of 1918 o and beyond the crest of its wave of incidence we saw relatively few patients with empyema As the curve declined i e toward the latter part of the outbreak empyema increased much in frequency Its character varied with the causative bacteria, the streptococci as a rule gave watery blood tinged exudates while pneumococci caused creamy exudates In many cases the exudate was more like a pleural effusion than an empyema but often in such many streptococci could be seen in smears appropriately stained

In these empyemata physical signs often were atypical and frequently it was very difficult to detect the change from consolidation to fluid The

persistent but dry is the rule Appetite loss is common, frequently with a queasy aching in the stomach Nausea and vomiting occur but infrequently, diarrhea is unusual except in children, where it may be a dominant feature Incidence of symptoms and signs[47] in 46 cases give an admirable bird s eye impression of epidemic influenza, dry cough 37 headache 32, chilliness 29 fever 27, sore throat 27, coryza 23, myalgia 18, malaise 14 anorexia 12 substernal pain 12, ocular myalgia 11, asthenia 8 vomiting 6, photophobia 4 hoarseness 3, otalgia 2, diarrhea 2, abdominal cramps 2, injected pharynx 37, injected nasal mucosa 30, suffusion of eyes 13 flushed facies 10 cervical lymphadenopathy 7 generalized lymphadenopathy 5 perspiring freely 3, injected tympani 3, pulmonary rales 4 pulmonary rhonchi 3 palpable submaxillary glands 2, prostration 2 sinus tenderness 1 palpable spleen 1, papular rash 1, nuchal rigidity 1 lethargy 1, delirium 1, lacrimation 1 Of course actual occurrence of these features will vary much in different epidemics

For most patients epidemic influenza runs a short course with fever for from 1 to 5 days not infrequently the fever being diphasic Symptoms rise rapidly to a maximum and then rapidly disappear In sicker patients respiratory symptoms and signs are more marked, in some of these bronchopneumonia ensues in all of these sicker patients the course is essentially as already described for pandemic influenza Leucopenia is the rule in epidemic influenza The urine often shows transient, slight albuminuria

Recovery as a rule is prompt without complications In some patients convalescence is followed by a period of physical and psychical depression as in so many of the patients in the 1918 20 pandemic

Clinical Course of Sporadic Influenza

The disease in scattered, isolated cases usually is like the mild forms of epidemic influenza Many however, are so mild as to make uncertain the diagnosis In fact only increase in anti body titer for virus A or B can make certain the diagnosis in these *sporadic cases*

Complications

These may occur in any of the varieties of influenza but are far more frequent in pandemic influenza Bronchopneumonia has been regarded as part of the disease *Lobar pneumonia* is infrequent but may be con

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persistence of bronchial breathing and bronchophony very often caused confusion for those less experienced with empyema. Decreased expansion on one side, cardiac displacement, decreased tactile fremitus, dullness, extending to the very base and with an upper border not corresponding to the line of separation between lobes, and egophony near the upper border of dullness are particularly suggestive signs of fluid. It cannot be too strongly urged that with signs at all suggestive of fluid, the exploratory needle should be used at once, for early diagnosis and prompt treatment are of the utmost importance to the welfare of the patient. X-ray, particularly fluoroscopic examination, of these patients is of very great assistance in diagnosis.

If free fluid presents diagnostic difficulties, you can well imagine the puzzling pictures that result from pocketed or interlobar empyemata. Careful observation of the progressive changes in physical signs, x-ray and the exploratory needle are required to make the diagnosis; stereoscopic x-ray films often are of very great help in this group.

Pleural effusion sometimes occurs in influenza, more often it appears during convalescence. It is to be diagnosed by the same means as those used for detecting empyema. When the trochar yields a serous fluid in these patients, it is important to examine it for bacteria, because, as already stated, some of the serous fluids contain abundant streptococci and patients of this group require prompt and proper treatment, if they are to recover.

Whenever an influenza patient continues to run his fever, and signs of pulmonary involvement are not clearing up, assume that fluid is present and make it your business to locate it. This is a good rule. Unresolved pneumonia does follow influenza with fair frequency, but most supposedly unresolved pneumonias are really something else, and many are empyemata of some form.

Mediastinal and *subcutaneous emphysema* has been referred to under "Pathology." Subcutaneous emphysema is recognized easily. It usually makes its appearance at the root of the neck just above the sternoclavicular region, but it may spread from this place both up and down and become so extensive as to obliterate the curves of the neck and puff out the skin. Over it pressure produces crepitation. When confined to the mediastinum, it is difficult of recognition except when in the tissue between pericardium and anterior chest wall; here it gives a curious, fine, crackling sound with the heart impulse, nearer the ear and crisper, more crackling than the sounds of pericarditis. Sometimes mediastinal em-

physema causes marked resonance on light percussion over the sternal region such as one gets over a pneumothorax

Pneumothorax occurs both in association with mediastinal emphysema and in association with empyema The former probably is not a very infrequent accompaniment of mediastinal and subcutaneous emphysema although as a rule unrecognized The latter is rare

Tuberculosis sometimes is caused to become active by influenza and following pandemic influenza a considerable number of spreading progressing tuberculous infections of the lung were seen Rarely the supposedly bronchopneumonia of influenza turns out to be a tuberculous pneumonia Per contra very often what is supposed to be tuberculosis has turned out to be the persisting signs of an influenzal peribronchitis slowly resolving pneumonia or a pocketed empyema. With both possibilities in mind careful discriminating observation will yield a correct diagnosis Very often however it requires time to determine which of these conditions one is dealing with X ray study here is very useful particularly repeated x ray examinations which enable us to watch changes in suspicious processes Obviously tubercle bacilli should be searched for in these patients long and often finding them makes positive the diagnosis of tuberculosis but does not exclude the post influenzal conditions already referred to, both may be present in the same patient

Cardiac Complications—These are infrequent Acute pericarditis occurs but as a rule this is with extensive pleurisy or empyema and in this association usually it passes unrecognized until revealed at autopsy Clinically detected pericarditis is infrequent Acute endocarditis is rare When these cardiac lesions occur any of the bacteria concerned in influenza as secondary invaders may be found Recognizable myocarditis is a great rarity except the slighter forms detectable by changes in the electrocardiogram These are not infrequent usually the electrocardiographic changes disappear Chronic cardiac disturbances following influenza are very infrequent All in all the heart bears a remarkable immunity to lesions during or following influenza

Vascular Complications—As with all infectious diseases some vascular lesions result but these are infrequent Intermittent claudication is reported presumably following some lesion vasomotor or organic narrowing the arteries to the leg Thrombosis of arteries occurs but is very rare venous thrombosis is seen more often Thrombosis of the saphenous vein is not infrequent mesenteric thrombosis may occur With each go disturbances depending on the vascular tree involved and the degree of impairment to local circulation With venous thrombosis pulmonary

persistence of bronchial breathing and bronchophony very often caused confusion for those less experienced with empyema Decreased expansion on one side, cardiac displacement, decreased tactile fremitus dullness, extending to the very base and with an upper border not corresponding to the line of separation between lobes, and egophony near the upper border of dullness are particularly suggestive signs of fluid It cannot be too strongly urged that with signs at all suggestive of fluid, the exploratory needle should be used at once, for early diagnosis and prompt treatment are of the utmost importance to the welfare of the patient X-ray, particularly fluoroscopic examination, of these patients is of very great assistance in diagnosis

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istics Most patients with influenza show no or only a slight febrile albuminuria and cylindruria

Influenza and Pregnancy —For the pregnant woman influenza is a serious disease A large per cent abort or miscarry In pregnancy the incidence of the bronchopneumonia of influenza seems higher than in the non pregnant and the mortality from it certainly is higher particularly in the later months of pregnancy In those who miscarry the infant as a rule is dead

Organs of Special Sense —Mild conjunctivitis is quite common Severe inflammations of the eye are rare Thrombosis of retinal arteries retina hemorrhage and post influenza optic atrophy are reported Acute otitis media is quite common Acute mastoiditis is seen less often The various accessory sinuses are found involved in a large per cent of autopsied cases and infection of these sinuses probably is a common occurrence I know of people who following influenza have a persisting sinus infection In these sinuses pure cultures of *H influenzae* may be found or there may be other pyogenic organisms A medical friend of mine says that since 1893 he has been daily blowing thousands of *H influenzae* bacilli from his nose but has no evidence that he has ever been a source of influenza to others

Nervous System Complications —Meningitis due to *H influenzae* occurs but is rare in epidemics of influenza More frequent is a meningitis due to pneumococci streptococci or staphylococci Brain absecess is reported Myelitis and Landry s ascending paralysis occur but these are rare The relation of influenza to encephalitis lethargica is discussed elsewhere (see Vol VI of Oxford Medicine) Following influenza psychoses of various types are met with Peripheral neuritis of varying types and extent may follow influenza

Skin Lesions —Erythema and cyanosis have been discussed Occasionally a measles like rash is seen Rarely purpuric spots appear Herpes labialis occurs in five to ten per cent of influenza patients Very small vesicles are not unfrequent on the soft palate and posterior pharynx Subcutaneous abscesses are not very uncommon Alopecia is frequent especially in women appearing usually four to six weeks after the attack Fortunately the hair grows back promptly Often after influenza the finger and toe nails are ridged and rough until they are replaced by new ones

Arthritis parotitis and other more unusual complications have been reported

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embolism and infarction may occur Of these, pulmonary ones are of importance, pulmonary embolism may cause death, or pulmonary infarcts with their usual signs may result

Gastrointestinal Complications —Nausea, vomiting and diarrhea occur rather infrequently as part of the symptomatology of influenza There has been much difference of opinion as to the occurrence of gastrointestinal influenza That in some epidemics gastric and intestinal disturbances are prominent is certain At times, following, or in association with an outbreak of typical influenza, there occurs a disease apparently contagious in which there are nausea, vomiting diarrhea and fever, sometimes with severe headache and pain in the back and legs The same things occur in epidemic proportions unrelated to influenza In all probability this has nothing to do with influenza but is a disease entity of other etiology Influenza virus A or B has not been demonstrated in connection with such forms of acute gastrointestinal disease The terms gastrointestinal influenza or gastrointestinal "flu' should be abandoned

Gastric and intestinal hemorrhages occur with influenza Appendicitis according to some statistics has increased immediately following the epidemic Jaundice appears with some of the cases especially those with pneumonia Cholecystitis and general peritonitis are reported as rare complications Abdominal pain is not infrequent in influenza and often presents much difficulty in diagnosis The pain may be general or localized to a region such as the gall bladder or appendix region With it there usually are tenderness and muscle spasm Sometimes it is due to peritonitis general or localized, at other times it seems to have resulted from the degeneration in muscles of the abdominal wall already described, leading to rupture of the muscle and interstitial hemorrhage, at least there was no evidence in these cases of peritonitis, appendicitis or cholecystitis With an existing pneumonia the abdominal pain may be a referred pain from involvement of the lower intercostal nerves as they pass beneath the pleura

Genitourinary Complications —Precipitated menstruation has been referred to Metrorrhagia at times is severe, prolonged and causes much loss of blood Orchitis is reported Pathologically the testes show aspermia and focal degenerations, the latter may be the starting point of the orchitis The only case I saw with this complication had a suppurating type of orchitis Hemorrhage from the bladder and from the renal pelvis has been observed Acute nephritis may follow influenza, but it seems to be very unusual When found it presents no special character-

in the exigencies of work in an epidemic period it is very likely that milder pneumonias escaped diagnosis and those diagnosed pneumonia in large part were patients with extensive involvement

What has been said of prognosis so far applies to pandemics of influenza as occurred in 1918 20 rather than to such epidemics as appear without pandemic spread The more usual localized type of influenza epidemic has a low mortality because pneumonia does not occur or remains mild Occasionally for some unknown reason the disease becomes more severe with frequent pneumonia in these epidemics mortality increases Roughly mortality rises in ratio to increase in prevalence of pneumonia in patients with influenza

Diagnosis

Influenza usually can be recognized by the general characteristics of the illness in the individual During an epidemic diagnosis is relatively easy Between epidemics diagnosis is problematic and many mistakes are made This is emphasized by the fact that the beginning of an epidemic almost invariably is diagnosed in retrospection after the epidemic is well under way An accurate diagnosis can be made only by isolating and identifying influenza virus by the intra allantoic inoculation of chick embryos with throat washings collected early in the disease or by appropriate immunological tests especially one that demonstrates an increase in specific antibody titer during or following an attack of influenza A readily available method for measuring influenzal antibodies is based on the inhibition by the patient s serum of the agglutination of chicken and certain other red blood cells in the presence of influenzal viruses Hirst s[48] original technic subsequently has been modified and simplified[49, 50, 51] Some of these methods should be used for the accurate diagnosis of influenza this is necessary in evaluating the results of methods of preventive vaccination

Prophylaxis

Influenza is a preventable disease that we cannot prevent that is to say it is a contact contagion preventable by absolute quarantine but practically its spread has never been prevented except temporarily in isolated communities because of the difficulty of recognition in its con

Prognosis

Influenza without bronchopneumonia is not fatal except possibly in very debilitated or very old people All fatal cases that I[2] observed had bronchopneumonia From this it follows that, if bronchopneumonia does not develop, prognosis is extremely good If bronchopneumonia ensues, prognosis varies with the extent of involvement There is a type with early diffuse pulmonary lesions, in essence an acute inflammatory edema of the lungs, in which prognosis is extremely poor These patients have an extensive cyanosis and a clammy cold, ashen gray skin When these are encountered few recover, so that these findings are almost surely indicative of death although fever may be slight and pulse and respiration not rapid It has been thought that prognosis in bronchopneumonia varies with type of bacteria being better with pneumococcus and worse with streptococcus hemolyticus but there would seem to be many exceptions to these statements, and it is very difficult to give any prognostic percentages depending on infecting bacteria or anything beyond such a general statement as that above An increasing rate of respiration is a bad prognostic sign in these patients, and the same is true of an increasing pulse on the other hand temperature has but little relation to prognosis Empyema makes prognosis much worse In civil hospitals in the 1918-20 pandemic the mortality was high, but here came only the worst cases and a very large per cent of the patients had pneumonia Figures for our military camps give a better index of bronchopneumonia morbidity and mortality in the 1918-20 pandemic The following table given by Soper[3], summarizes very well conditions as they existed in the military camps in the United States from September 12 to October 18 1918

	September		October			Total
	20	27	4	11	18	
Influenza	10 094	37 493	88 478	90 393	48 287	274 745
Pneumonia	758	4 313	8 655	17 88	14 768	46 86
Deaths	96	951	2 275	6 005	5 289	14 616

From this we see that of 274,745 cases of influenza 14,616 died It is fair to assume that practically all of these had pneumonia. It is also fair to assume that more than the 46 86 probably had pneumonia for,

people are more often condemned than advised as preventive measures against influenza My feeling is against advising their use

Vaccination Against Influenza

The use of killed bacteria in the form of vaccines containing various organisms have been disappointing in prophylaxis[21, 26] Measures for effective immunization against influenza are needed if influenza epidemics are to be prevented or at least lessened in their morbidity and mortality To accomplish this first were needed methods for growing the virus of influenza in large amounts and next for concentrating and purifying the virus and vaccine made from it to a degree making permissible relatively safe introduction into human beings Both of these now are possible The virus can be cultivated readily in the allantoic fluid of the chick embryo The virus grown in this allantoic fluid can be adsorbed by the erythrocytes of the embryo and then readily eluted from the red blood cells[49] Francis and Salk[50] devised a simplified method for the preparation of a concentrated and reasonably purified vaccine containing approximately equivalent amounts of influenza virus A and B Numerous studies of serological responses have been made[48, 49, 5] and this vaccine was found capable of stimulating production of specific antibodies and of actively immunizing mice Also it produced specific antibodies in human beings and caused protection[3, 54] Vaccines so produced now have been tested out extensively in man and they have been shown to have definite protective influence against both influenza A and influenza B Vaccination against influenza B in the autumn of 1945 showed a ratio of cases in vaccinated versus unvaccinated of 1 to 9[56] Protection also has been reported for influenza A[1, 66, 7] Much more investigation is needed to determine such important items as the best form of protective vaccine to use in what doses and at what intervals time needed to develop maximum protection duration of protection etc It seems probable that protective vaccination against influenza will be developed further and become the one efficient and effective method in prophylaxis of influenza

One feature of these protective vaccinations must be considered The virus is grown in the allantoic fluid of eggs and so contain traces of egg white which is a highly allergenic substance to which many people have sensitivity This has been studied by Ratner and Untracht[8] They point out that all persons should be tested intradermally with 0 0 c c of undiluted vaccine before administering each and every prophylactic dose

tagious stage and its very rapid spread through the country Reduction of personal contacts should reduce contagion, and all general prophylactic measures are based on this assumption Prevention of close contact in cars, dance halls, churches and places of amusement etc are the chief measures adopted How effective such measures actually are has been questioned The trouble is that they are almost always put into effect after the epidemic has made much headway, and the measures are not strictly enforced, in part from the almost complete impossibility of carrying them out under urban conditions and in part because of impossibility of securing thorough cooperation from a minority of the population These are not sufficient reasons however, for condemning the attempt or for saying that prevention is impossible Moreover, these efforts may have considerable effect in reducing the spread and speeding the stamping out of the epidemic, and I think they should be carried out as thoroughly as possible Individuals at times of epidemic should avoid crowds keep in the open air as much as possible, go to bed early and eat simple, nutritious food All community measures that decrease crowding together of people should be encouraged

Masks have been extensively recommended They have been used in large communities under compelling laws It is very questionable whether large scale use is desirable To be effective the mask must be of several thicknesses of gauze[41] and must be changed often enough to prevent wetting through from saliva Gauze that has been washed many times is a much more efficient filter of bacteria than is new gauze Six layers of gauze 42 by 42 strands per inch, washed 20 times has a filtering efficiency of 97 per cent Certainly they do no good, when fingers often make their way under them as so often happens They are used to prevent droplet infection when influenza-stricken people sneeze or cough This protection would be better afforded if all citizens covered mouth and nose when sneezing or coughing This latter should be insisted on vigorously As to masks, I believe that community use should not be advised For those coming in contact with patients I think masks have a use in part protective, in part a reminder of the danger and how to avoid it Still we must confess that deliberate effort to infect normals by having influenza patients cough or sneeze in their faces failed, and so skepticism as to any need for masks for those handling influenza patients is justifiable If not protective against influenza they may keep out pyogenic organisms that have become enhanced in virulence and so in that way reduce the incidence of respiratory infections

Antiseptic nasal and throat sprays washes and douches for well

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If the test is negative or suggestive, the vaccine can be given with impunity, if the local reaction is moderate, the vaccine can be administered with the precaution of using simultaneously 0 12 to 0 18 c c of epinephrine If the local reaction is a large one, the vaccine should be given only in divided doses at 1, 2 or 3 day intervals preceded by epinephrine If a test dose causes a systemic reaction, the vaccine should be withheld unconditionally The need for such precautions is shown by the report of a fatal allergic reaction to influenza vaccine[59]

Treatment

For influenza there is no specific Quiet in bed and good nursing are of more value than anything else All influenza patients should go to bed at the onset of the disease and remain there until the temperature is normal throughout three days There should be no periods out of bed for the patient until his temperature has been normal for three days Such vigorous treatment should be insisted on even for very mild cases, for it seems from experience in the 1918 epidemic that this is the surest way of preventing subsequent bronchopneumonia

Diet in all forms of influenza should be simple and nutritious and forced enough to give 2,500 to 3 000 calories per day Liquids should be at least 2 000 c c daily With nausea and vomiting it is, however, very difficult to feed any such amount, fortunately these symptoms usually do not persist

Acetyl salicylic acid (aspirin) in 0 6 gm (10 grains) doses or phenacetin in 0 3 to 0 6 gm (5 to 10 grains) doses every four hours are of value when there is headache backache or pain in the muscles Dover s powder, 0 3 to 0 6 gm (5 to 10 grains) is helpful for the first few nights It is rare that morphine is needed it should only be used when pain is very severe Mild saline catharsis is advisable in the beginning Drugs should be used but little for simple influenza

Bronchopneumonia or pneumonia, if present, should be treated with chemotherapy appropriate to the causative bacterium For chemotherapy at present there is available a sulfonamide preferably sulfadiazine, penicillin and streptomycin using the one most effective on the causative bacterium Cardiac stimulants seem to me to have been of no value, and in this many concur Expectorants have no place In the early part of the epidemic we bled some patients with cyanosis, but it did no good Oxygen inhalation at times relieves cyanosis, it should be used as advised

in the treatment of pneumonia or bronchopneumonia of any etiology

The only new form of treatment developed in the 1918 epidemic was the use of serum pooled from convalescent cases of influenza broncho pneumonia with negative Wassermann reactions as advocated by Redden and others This has been supported enthusiastically by many observers while others remained skeptical of there being any striking results Soon after 1918 in Oxford Medicine I wrote as follows from a review of the literature and realizing the great difficulty in evaluating any form of treatment in pneumonia such as is associated with an influenzal epidemic I myself am of the opinion that the method is of relatively little value' This opinion seems justified by subsequent studies and clinical reports

So far no effective serum for treatment of influenza has been developed

Empyema should be diagnosed early and treated promptly either by chemotherapy or surgical drainage as described elsewhere in Oxford Medicine where various forms of pneumonia with complicating empyema is discussed

The numerous complications require such treatment as would be given for these conditions whenever met with that they occur in influenza does not alter in any specific way their treatment

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CHAPTER XXVII-A

EPIDEMIC MYALGIA EPIDEMIC PLEURODYNIA BORNHOLM DISEASE

By HENRY A CHRISTIAN

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Synonyms — Myositis epidemica myalgia epidemica infectious pleurodynia epidemic diaphragmatic spasm epidemic phrenic neuralgia Devil s grip Born holm disease Eyderstadtchekrankheit Stoppelfieber Bamble disease

Definition — This is an acute infectious disease apparently of virus etiology of short duration with fever headache paroxysmal pain in a muscle group or groups in a very surprising way almost always being limited or almost limited to the diaphragm group of muscles and sometimes showing symptoms of involve ment of the central nervous system

HISTORY AND INCIDENCE

Our first knowledge of this disease seems to date from George Hannaeus or Hannes who described an extensive epidemic that occurred in 1732[1] This dis ease has such a striking simple symptomatology that its recognition from old clinical descriptions is so easy as to render its history of past occurrences very definite[1 2] Its recognition as a disease entity usually is ascribed to Daae[3] in a

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paper published in 1872, but it is hard to believe that any observer of an epidemic of it failed to recognize that he was seeing a very definite disease entity, what ever name he used for it In the same year Homann also described 100 cases in Norway In 1874 Finsen[4] described outbreaks of it in Iceland which had occurred there in 1856 and 1863 he gave the name to it of epidemic pleurodynia In 1926 565 cases were recorded in Iceland This disease is said to be endemic on the island of Bornholm off the coast of Denmark, and Sylvest estimates there had been 10 000 cases of it in Denmark from 1930–34 In 1789 occurred a great epidemic in Switzerland but it had no recurrence there for over 100 years In 1897 in Norway 4158 cases were recorded

A wide distribution of this disease is indicated by many published reports which are to be found in the Scandinavian German Swiss, Portuguese, Finnish British and American medical journals An early report of it in the United States is that of Dabney who reported on an outbreak in Virginia[5], spoke of it as devil s grip and indicated its resemblance to dengue Since then it has been reported from many states in the United States Since very typical epidemics have occurred in college populations with evidence of very rapid spread, it is noteworthy that so far it has not been prevalent in our military forces, where so many young men have been brought into similar close or even closer association Had it occurred in our armed forces to any extent with its characteristic sudden onset and typical painful symptoms it seems unlikely that it would not have been reported, but so far the only reports that I have found are those of Williams[31] of 5 rather atypical cases in soldiers in England and that of Abel[37] of a small outbreak (32 cases) of typical cases in the Royal New Zealand Air Force, no cases seem to have been reported as occurring in the allied armed forces in World War I

Etiology and Pathology

In epidemic outbreak and rapid spread from individual to individual epidemic myalgia or pleurodynia behaves like a virus disease with a probable air borne distribution to those coming in close contact with individuals sick of it The occasional report of central nervous system symptoms[36 33], with or without pleocytosis of the spinal fluid is consonant with a virus etiology as are the failures to demonstrate bacteria of any sort in spinal fluid, blood or mouth and nasal washings Attempts to reproduce the disease in animals, hamsters monkeys mice guinea pigs and rabbits or to grow the virus in embryonated egg or media containing cells of human derivation have failed so the virus etiology remains only an assumption although it is a distinct probability Small s[11] claim in 1924 of finding a plasmodium in the red blood cells which he called *Plasmodium pleurodyniae* has had no confirmation, and so in

fairness it can be disregarded as the cause of epidemic myalgia or pleurodynia Various authors[illegible] have discussed an apparent association of the clinical picture of this disease with choriomeningitis with influenza with dengue and with poliomyelitis all virus-caused diseases an additional suggestive evidence of virus etiology for it Apparently no direct transfer of this form of myalgia from man to man has been attempted using filtered spinal fluid or nasal or mouth washings as proof of its cause by a small filter passing organism either virus or rickettsia One such attempt with whole blood failed[16] So far complement fixation or other serum reactions have not been demonstrated in recovered cases and no complement fixation tests have been obtained to indicate antigenic relationship to the virus of influenza poliomyelitis or of lymphocytic choriomeningitis In other words although probable there has been produced no positive evidence of virus etiology of infectious myalgia or pleurodynia Cold hemagglutinins do not develop

Of the pathology of the disease we know almost nothing Fatalities do not occur and biopsy of the diaphragm is hardly a feasible diagnostic procedure In one patient[18] a bit of apparently involved latissimus dorsi muscle was excised and studied histologically but no changes in it were found under the microscope By the terminology some assume the existence of an inflammatory process in muscle or nerve but beyond this there has been no commitment to date as to the pathology of a disease so variously named as this a variety in terminology fully justified by our ignorance of what goes on in muscle or nerve to cause such striking symptoms

Epidemiology

Epidemic myalgia or pleurodynia spreads rapidly once the disease begins This is well shown by the studies of Locke and Farnsworth[illegible] of the spread of an epidemic of 1[illegible]1 cases at Williams College Williamstown Mass in 1935 where the explosive nature of the epidemic was very striking Fifteen per cent of the student body developed the disease which indicates the highly contagious character of it This is still better exemplified by its occurrence in fraternity houses in which inter student contacts would be very close in these houses incidence ranged from 0 to 64 7 per cent At Williams College the outbreak was of a character and distribution and in a location that would make insect transmission almost without any probability but it does suggest very strongly patient to patient distribution of the disease by quite close contact much as happens in the spread of influenza It is of great interest too that epidemic myalgia or pleurodynia in this same period had a very high incidence in a nearby city North Adams where it is estimated that 600 to 700 cases developed Also there were numerous cases in Williamstown outside of the student population and in other towns in this region Two years before this period there was an extensive outbreak in Bos

ton[14, 17] at the other end of the state In general, incidence in most reported epidemics has been highest in children, Locke and Farnsworth stating that "available figures indicate that approximately 37 per cent of all cases occur under fifteen years of age Occurrence in families[9] has been noted in a number of reports

Symptomatology and Clinical Course

Cases of epidemic myalgia or pleurodynia present a most striking clinical picture Abruptly, often with no prodromata, a previously well patient experiences pain in the upper abdomen or lower level of the thorax, centered at about the line of attachment of the diaphragm to the thoracic cage Rarely there may be antecedent mild headache, slight malaise or nausea The pain may be mild or extremely severe in the majority of patients severe rather than mild Pain may develop in an individual who prior to its appearance is feeling in normal condition and be so abrupt and severe as to render it difficult for him to get to a place for rest or medical help No special factors seem to have any part in precipitating the attack, attacks begin at any time during the day or night, while at rest or during physical activity during meals or between them

Pain is the main symptom It usually is located in the region of the attachment of the diaphragm More often it is distributed on both sides of the body rather than being unilateral in distribution However, bilateral pain may not be simultaneous but alternating in its appearance Anything that increases movements of the diaphragm such as sneezing, coughing, laughing, deep breathing or exercise increases the pain The patient to relieve the distress does various things as assuming a fixed position such as leaning over a chair or table, sitting or lying as relaxed as possible bent to one side or the other, holding the body as rigidly as possible If he must walk, he moves slowly and deliberately

Pain, localized as already described may have various radiations such as across the lower abdomen or along its sides into the lower or upper back, up into the sides of the neck to the tops of the shoulders, the front of the chest even down the legs These radiations may be sharply localized to areas not more than a few inches in diameter, where slight hyperesthesia can be demonstrated The pain is described as cutting knifelike, paroxysmal

It is interesting that muscle tenderness seems lacking although muscle spasm and cutaneous hyperesthesia are present The abdominal symptoms and findings may simulate those from an acute intra abdominal lesion such as appendicitis or gall bladder but such incorrect diagnosis with subsequent operation has been rare

Fever is almost as constant a symptom as pain As a rule, there is a sharp rise in temperature to 103° to 104° F with onset of pain Fever persists usually for 24 to 48 hours or even a shorter time and then subsides quickly It will recur,

if the pain recurs In some severe cases irregular pyrexia lasts for 10 to 14 days Chills are common in the severe cases in 39 of Locke and Farnsworth s 121 cases with chilly sensations in another 12 There may be a succession of chills Sweating is common with and without chills

Headache is the third in the triad of usual symptoms and may be slight moderate severe or violent so described in 11 29 20 and 16 respectively of 76 of the 121 cases described by Locke and Farnsworth In some patients headache absent at first appeared with exacerbation of the pain and fever This headache usually is decreased promptly by analgesics and local applications of cold The headache is described variously as heavy feeling aching throbbing pressing bursting boring etc Its location oftenest has been in the frontal region It is little affected by position or movement of the head

The pulse is increased in rate in proportion to the fever Respiration is surprisingly little accelerated Gastrointestinal symptoms, nausea vomiting diarrhea occur but are infrequent except in children Mild conjunctivitis and reddened and somewhat sore throat may occur Hiccup and herpes are rare Nervous symptoms are described under Complications

Physical examination usually gives no evidence of pulmonary, pleural pericardial cardiac or peritoneal involvement in the process Rarely a pleural friction rub is heard pericardial friction is still more infrequent X ray of the chest shows no departure from normal There are evidences of great suffering anxiety and sometimes collapse Various positions are assumed in the effort to immobilize the diaphragm and relieve pain A transitory erythematous rash ha been reported Moderate leucocytosis may develop but leucopenia seems more frequent

In many patients duration is but 24 to 48 hours with quick relief from symptoms and complete recovery in a few days except for some occasional twinges of pain on respiratory exertion and too active physical exertion However in some patients recurrences of symptoms appear on the third or fourth day of freedom from symptoms In Locke and Farnsworth s 121 cases 45 had no febrile or pain recurrences 32 had 1 35 had 2 and 9 had 3 Duration of illness as would be expected is longer with remissions or recurrences In 25 of the patients of Locke and Farnsworth duration was 3 days or less 1 day in 8 patients 2 days in 12 and 3 days in 5 patients In the 45 patients with no exacerbation the average duration was 7½ days 3 lasting more than 12 days In the 32 patients with 1 exacerbation average duration was 10 6 days with 9 lasting over 12 days In the 35 patients with 2 exacerbations the average duration was 12 5 days with 10 lasting over 12 days In 9 with 3 exacerbations the average duration was 18 6 days with only 1 lasting as little as 8 days In a few patients convalescence was prolonged to one to several months

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might be regarded as part of the disease rather than as complications but as they occur infrequently they have been treated as complications

Other reported complications include pleurisy and pericarditis as well as mild conjunctivitis pharyngeal irritation and inflammation already referred to as well as orchitis and otitis media Moderate eosinophilia (over 3 per cent) was found in 105 of 114 cases[78]

Diagnosis

The clinical picture as already described is so definite as to make diagnosis very easy when with it consideration is given to the usual absence of physical signs and x ray evidence of inflammatory disease of the respiratory tract Confusion with dengue seems unlikely as the pain of that differs in distribution so as to present a dissimilar clinical picture and with dengue usually there is a skin rash while in epidemic myalgia or pleurodynia only infrequently does a rash occur

Prognosis

Prognosis is very good Fatalities do not result and in most patients recovery is prompt and complete The possibility of late disability from an accompanying meningoencephalitis should be considered but I have seen no report of such, although I have seen one patient with marked disabling parkinsonism who gave only a history of a very painful pleurisy many years back in his history as a possible cause of the parkinsonism however his story did not indicate any accompanying meningoencephalitis Second attacks in a second or third year have been reported but only infrequently suggesting that an attack confers considerable immunity

Treatment

No treatment beyond simple analgesic measures to abate the pain is indicated Without advice in that direction these patients are likely to remain in bed or stay quiescent in a chair during the period of pain and this restriction is desirable Sulfonamides penicillin and streptomycin have been used but were ineffective Aureomycin would seem well worth trying with the known good effect in non-bacterial pneumonias

In severe cases delirium may develop followed by weakness and dizziness The knee jerks and possibly other reflexes may be diminished or lost during the acute stage with return to normal on recovery

COMPLICATIONS

Symptoms and signs of nervous system origin have been absent from many descriptions until recently Now they begin to appear and will be considered as complications Sylvest (1933) mentions a case of encephalitis in one of the Swedish epidemics while Rehsteiner[34] (1941) says meningoencephalitis was prominent in an epidemic in Weisen, Germany In Cincinnati in 1935 [3] there were coincidental outbreaks of lymphocytic choriomeningitis and epidemic pleurodynia, and a relationship to poliomyelitis has been suggested In 1941 Williams[31] reported in 5 English soldiers with myalgia most severe in the trapezius muscles the occurrence of nuchal rigidity positive Kernig s sign and in 2 an excess of lymphocytes in the spinal fluid In the Brooklyn epidemic occurring in 1942[36] there were 5 patients out of a total of 166 with meningoencephalitis characterized by headache apathy vertigo and photophobia Some had mildly stiff neck 1 a positive Babinski reaction A pleocytosis of 37, 72 73 and 261, mostly lymphocytes was found in each of 4 patients Generalized convulsions are not infrequent in children under 2 Recently (1945) a small outbreak of 16 cases in a training school for nurses in Philadelphia[35] has been reported in 13 of which nervous system symptoms were present, and in 3 of these there were found spinal fluid abnormalities In these patients headache was more severe and much more difficult to control than had been usual in other outbreaks Photophobia was present in 6 along with the headache Several of the patients complained of unusual sensitivity to noise and mechanical vibrations suggesting possible hypothalamic involvement Haziness of the optic disc was a common finding to return to normal a week or two after recovery, suggesting increased intracranial pressure Hyperesthesia of thorax or legs was found in 13 of the 16 photophobia and nuchal rigidity in 12 positive Kernig s sign in 1 and bilateral patellar clonus in 1 Spinal fluid findings were as follows in the patients on whom it was done 20 lymphocytes and 155 cm H O pressure in 1 76 lymphocytes 150 cm H O pressure and 24 4 mgm protein per 100 c c in 1 no cells, 150 cm H O pressure and 30 mgm protein in 1, no cells 230 cm H_2O pressure and 45 mgm protein in 1 and 1 lymphocyte 145 cm H O pressure and 28 mgm protein in 1 In all these spinal fluid cultures were negative In 3 of these patients the author considered that the findings indicated a meningoencephalitis

All of this has pointed to the probability of at least occasional central nervous system involvement Such nervous system symptoms as those just described

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CHAPTER XXVII-B

NON-BACTERIAL PNEUMONIAS

By HENRY A CHRISTIAN

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Definition — Under the term non bacterial pneumonias are grouped for description patients with the symptoms and signs of pneumonia usually of the lobular rather than lobar type in whom blood cultures and sputum examinations fail to show evidence of a bacterial etiology Various other names[2–27] have been used for this type of disease such as *acute pneumonitis virus pneumonia* and *pneumonitis virus like pneumonia* and *pneumonitis primary virus pneumonitis atypical pneumonia bronchopneumonia of unusual character and undetermined etiology broncho pneumonia of mild severity bronchopneumonia of unknown etiology* (*variety x*) *atypical virus pneumonia an epidemic disease of the respiratory tract acute diffuse bronchiolitis, acute interstitial pneumonitis* Although this multiplicity of names is awkward and confusing for bibliographic study the various names taken together actually describe very completely in few words the chief characteristics of this disease namely a pulmonary process of inflammatory nature a febrile infectious disease of epidemic character a probable virus etiology and if not at least a non bacterial cause

INTRODUCTION

The etiology of this form of pneumonia is various but the clinical picture is much the same whatever the etiology In some there is evi

dence of a virus cause in others a rickettsia has been found in still others a toxoplasma organism occurs in very many no causative organism has been demonstrable So for the present an inclusive somewhat generic name has been used non bacterial pneumonias with further study probably definite etiological types will be distinguished and possibly there may be a clinical picture for each definite enough to permit of a clinical differentiation of various forms of these non bacterial pneumonias

History

Clinicians whose experience goes to the time prior to the 1918 epidemic of influenza very generally recognized that with influenza a form of pneumonia lobular in distribution for the most part with symptoms and extent of lung involvement in excess of physical signs of consolidation was common as was shown by x ray examination and postmortem study and that subsequent to this period there was a decreased frequency of typical lobar pneumonia and an increased frequency of what came to be termed atypical forms of pneumonia In many of these patients seen after the 1918 epidemic sputum failed to show pneumococci of type I and type II but did show type III pneumococci and undetermined types then grouped as type IV pneumococci or streptococci not infrequently bacteria were very sparse in their sputum Possibly these atypical pneumonias of the years following the 1918 influenza epidemic were in part at least the same as the variety under discussion in this chapter although not then of even mildly epidemic distribution In studying these patients always was there a difficulty in distinguishing them from post influenza pneumonia in some fatal case the lungs might show the appearances regarded as reasonably typical of the influenza process i e showing hyaline transformation of bronchiolar and alveolar mucosa Not until a virus had been demonstrated in influenza methods had been found to determine antibodies against it in the serum of patients and neutralization tests for it had been worked out was it possible to make a diagnosis with certainty of influenzal pulmonary disease this was accomplished after 1933 when Smith Andrewes and Laidlaw had demonstrated the virus of influenza and chiefly in the period 1939 to the present Only in the past few years have such studies clearly separated influenza from an other variety or other varieties of the epidemic pulmonary disease here being described and real progress been made in the investigation of non bacterial pneumonias

However it was some years after 1918 before cases of the type of

epidemic disease being discussed in this chapter were recognized and described probably not so much because they did not happen but because they were considered to be moderate epidemics of influenza

Beginning with 1935 reports of this form of pneumonia appeared at first from army camps and schools where young adults gathered in close daily contact later from urban populations In 1935 Bowen reported such cases as *occurring in 1932 and 1933 in the army in Hawaii* and in 1936 Allen[3] described similar patients from Fort Sam Houston in Texas

At about the same time Gallagher described cases in a boys school Later cases were reported from the student body of the Univ of Oregon[13] Oregon State College Stanford Univ Cornell Univ [1] and Harvard[13] and from the personnel of Jefferson Hospital Philadelphia[7 16 19] It has been reported too from Texas[17] Philadelphia[19] Baltimore[4 34] New York[23] *Boston*[25] *Ohio Minnesota Missouri Illinois* Cases *also have been* reported from England and from France It is not certain that all of these reports deal with the same disease but there is enough clinical similarity to suggest this A wide geographic distribution of it is evident

Etiology and Epidemiology

A *single causative organism for this group of patients has not been* demonstrated There seems sufficient evidence from sputum examinations and a few postmortem studies of the lung to justify the statement that they do not have a bacterial etiology From a few cases a filterable virus has been isolated by inoculation of ferrets but it could not be maintained for *specific protection and other tests to verify its etiological significance* From the majority of the cases no filterable virus could be isolated by ferret inoculations or other means This and other evidence point to this disease as not being caused by influenza virus A or B From patients with a clinically similar if not identical disease Weir and Horsfall[70] using the wild mongoose demonstrated a virus *which seemed to be the etiological factor in this group* of patients Studies of an epidemic of respiratory disease with associated pneumonitis at the National Institute of Health in Washington D C showed the *rickettsiae* of Q fever[70 21 30] Hesdorfer *and Duffalo*[28] *have* reported a probable case of Q fever from Montana Eaton and his associates[33] and others[34 37 38] have isolated a psittacosis like virus from patients and shown its widespread in pigeons[36 37 39] this disease has been named ornithosis (see Oxford Med Vol V Chapt XVIII-A A) Besides being contracted *from sick pigeons*[36 38 41] *and chickens*[37] *possibly cats*[43] *and dogs*[41] *having a*

dence of a virus cause in others a rickettsia has been found in still others a toxoplasma organism occurs in very many no causative organism has been demonstrable So for the present an inclusive somewhat generic name has been used non bacterial pneumonias with further study probably definite etiological types will be distinguished and possibly there may be a clinical picture for each definite enough to permit of a clinical differentiation of various forms of these non bacterial pneumonias

History

Clinicians whose experience goes to the time prior to the 1918 epidemic of influenza very generally recognized that with influenza a form of pneumonia lobular in distribution for the most part with symptoms and extent of lung involvement in excess of physical signs of consolidation was common as was shown by x ray examination and postmortem study and that subsequent to this period there was a decreased frequency of typical lobar pneumonia and an increased frequency of what came to be termed atypical forms of pneumonia In many of these patients seen after the 1918 epidemic sputum failed to show pneumococci of type I and type II but did show type III pneumococci and undetermined types then grouped as type IV pneumococci or streptococci not infrequently bacteria were very sparse in their sputum Possibly these atypical pneumonias of the years following the 1918 influenza epidemic were in part at least the same as the variety under discussion in this chapter although not then of even mildly epidemic distribution In studying these patients always was there a difficulty in distinguishing them from post influenza pneumonia in some fatal case the lungs might show the appearances regarded as reasonably typical of the influenza process i e showing hyaline transformation of bronchiolar and alveolar mucosa Not until a virus had been demonstrated in influenza methods had been found to determine antibodies against it in the serum of patients and neutralization tests for it had been worked out was it possible to make a diagnosis with certainty of influenzal pulmonary disease this was accomplished after 1933 when Smith Andrewes and Laidlaw had demonstrated the virus of influenza and chiefly in the period 1939 to the present Only in the past few years have such studies clearly separated influenza from an other variety or other varieties of the epidemic pulmonary disease here being described and real progress been made in the investigation of non bacterial pneumonias

However it was some years after 1918 before cases of the type of

and in hospital personnel Where contacts can be dated a long incubation period of 14 to 21 days can be made out[23, 24] This is in sharp contrast to influenza for which in epidemics incubation period is short averaging 2 days

Pathology

X ray studies indicate the presence of pneumonic consolidation except in the very mild cases This is of lobular type Fatalities have been infrequent and so there are not many studies of the pathology Kneeland and Smetana[3] describe post mortem findings in 1 case Longcope[4] in 2 both of the latter complicated by occurrence in patients with rheumatic heart disease Kneeland and Smetana[3] describe the lungs in their case as follows The consistency of the lung tissue varied in different parts there were many small airless patches which projected slightly above the surface and the intervening air containing lung tissue appeared moderately emphysematous On cross section salmon pink and gray areas of consolidation varying in size from a few millimeters up to less than a centimeter were scattered through the parenchyma and occasionally appeared to be confluent The cut surface was quite dry The bronchi contained thick mucopurulent exudate and their mucosa was congested

Longcope[4] has summarized his findings thus The pathology of the disease is quite as distinctive as the clinical course The lungs show lobular solidification deep red in color often moist and involving a fairly large portion of one or more lobes The smaller bronchi may contain a great deal of pus Sections show a rather peculiar form of pneumonia The bronchi may be filled with cells usually mononuclear with scattered polymorphonuclears In two cases we noted metaplasia of the epithelium lining the alveolar walls The exudate in the alveoli consists of blood coagulated serum and mononuclear cells with some large macrophages There is no fibrin formation

Discussing the histological picture Kneeland and Smetana write as follows The interesting feature of this case is the peculiar type of pneumonia of which various stages are seen in the section the earliest stage is characterized by a hemorrhagic exudate which later is succeeded by an exudate composed chiefly of mononuclear cells with a marked tendency to organization Other features are the appearance of large mononuclear cells at the periphery of the alveolar spaces forming rows which gradually line the new narrowed lumina and the fatty changes of the exudate cells There is an acute interstitial bronchitis or tracheitis with abundant production of mucopurulent exudate The lesions in the

pneumonia like disease may cause it Adams[31] and also Goodpasture[1] have shown cell inclusions pointing to a virus origin in pneumonitis of infants The virus of lymphocytic choriomeningitis has been isolated from an influenza like disease in which there were no neurological lesions Pinkerton and his associates have demonstrated toxoplasmosis in patients with pulmonary reactions very similar to those in patients under discussion in this chapter (see Oxford Medicine Vol V Chapt XXXVI–A)

This brief review of investigations on the etiology of respiratory diseases that can be grouped together under the term non bacterial pneumonitis because of their similar clinical manifestations indicate that not a single but several different non bacterial organisms are causative Since only very few of these epidemics have yielded definite evidence as to etiology one can not say with certainty what the etiology is Since already there have been isolated from patients with clinical influenza two viruses A and B (see Oxford Medicine Vol IV Chapt XXVII) even from patients in the same epidemic and since also clinical influenza occurs without evidence of the presence of either influenza A or B virus it is entirely possible that the form of pneumonia here discussed may prove to be divisible into several etiological varieties including some caused by the virus of influenza However the clinical course and the incubation period of cases of this group of pneumonias make it probable that they can be distinguished from pneumonia of influenza virus origin If this is so then it seems reasonable to say that the cause of this group after separating out cases of rickettsia or toxoplasma etiology is a virus very possibly of more than one type as indicated by the preceding discussion

Numerous diseases such as measles scarlet fever variola chicken pox mumps etc recognized to be caused by viruses develop in some patients pulmonary lesions of pneumonic type during the course of the disease just as others of them develop the cerebral lesions of encephalitis This increases the difficulty of diagnosis and classification of patients with non bacterial pneumonia It seems reasonable however to classify as pneumonia those patients in whom pulmonary symptoms and signs are prominent and skin rashes etc are little in evidence and to regard the pneumonia in the others as a complication Finally, we must remember that general diseases of virus etiology do develop bacterial pneumonia as a complication and such pneumonias need to be treated as such

Published reports indicate that non bacterial pneumonias are communicable diseases transmitted by direct contact This is indicated by their appearance in army personnel in schools colleges and universities

which the disease progressed it is convenient to describe in more detail its course in those patients who experienced a mild attack (12 cases) those that had a moderately severe attack (11 cases) and those who were severely ill or died (9 cases)

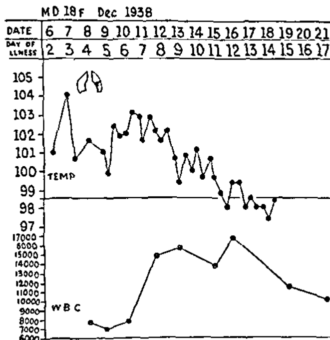


CHART I This patient female age 18 began recovery on 18th day of illness and lungs were clear on 23rd day recovery was complete Note in chart relation of leukocyte count to fever and note also lung involvement (From Longcope)

Of the 12 cases in the first group one half (6) had been in contact immediately prior to their illness with patients suffering from a similar variety of pneumonia Though all 12 had fever cough and malaise most had very little sputum and none of them appeared or felt ill for more than three or four days Herpes labialis was not noted Sweats were frequent in some of these patients In one patient the sputum was slightly blood streaked on two or three occasions and one patient had a pharyngitis due to beta haemolytic streptococci As the disease proceeded most patients showed some physical signs of involvement of the lungs In 3 patients however repeated examinations disclosed only a few rales over the left lower lobe In all the others there was noted very slight to moderate dullness often suppression of breath sounds and always râles

walls of the medium sized branches of the pulmonary artery have the character of peri arteritis nodosa in its acute form and are all apparently rather recent No similar lesions were found in other viscera which is all the more surprising since peri arteritis nodosa of the pulmonary artery is not at all common The question thus arises whether the vascular changes are the primary factor or are a complication of the pneumonia In favor of the assumption that the two processes are separate is the point that the pulmonary changes in many places appear less acute and recent than those of the pulmonary arteries

Although there has been so little opportunity for examination of the lung these two reports indicate a pulmonary process very different from that found in bacterial pneumonia and also unlike that found in influenza More fatal cases must be studied before it is known whether the findings of Kneeland and Smetana [3] and of Longcope [4] can be considered as typical of this condition

Clinical Course

In many patients illness begins as an upper respiratory tract inflammation seemingly spreading from patient to patient by contact soon to reach epidemic proportions as shown at the Jefferson Medical College and Hospital in Philadelphia [19] where of 813 persons 407 became ill of these 75 per cent remained ambulatory and 25 per cent became bed patients The ambulatory patients complained of such symptoms as coryza nasal obstruction malaise frontal headache weakness dizziness sweating and anorexia Dry cough appeared occasionally Fever was slight or absent They were sick one to several days some had one or two relapses in which they were apt to be sicker Of the bed patients in this epidemic 25 were considered by Reimann and Havens[19] to have tracheobronchitis and 25 tracheobronchopneumonia In New York [3] and Baltimore [4] the patients seem to have been sicker than in Philadelphia possibly because the studies were confined mainly to hospitalized patients among them pulmonary parenchymal involvement was almost the rule The New York and Baltimore patients were separated in each report into three clinical groups according to severity of illness

Longcope's[24] description which follows gives a very satisfactory picture of the disease when the lower respiratory tract is involved (see Charts I–IV)

The onset of the disease was similar in most of the patients but the subsequent course varied greatly from a mild infection to one which was extremely grave or fatal In order to give some idea of the manner in

IV) In the mildest forms the temperature fell from 103° or 102° on the third to fourth day of the disease to reach normal through slight fluctuations by the fifth to the tenth day. But in several instances in which the febrile course was more prolonged there was a preliminary rapid drop in temperature followed by a secondary rise with an irregular

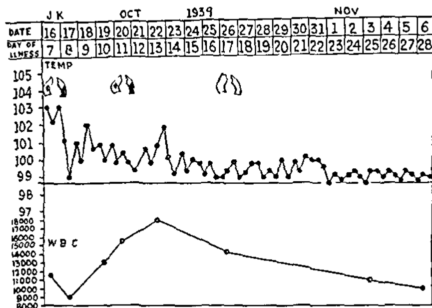


CHART III A female age 3 was moderately ill with fever lower than many of the patients The chart shows cou e of illne s Note lung involvement and course of leucocyte count Recovery was compl te (From Longcope[2])

defervescence the temperature declining to normal on the twelfth to sixteenth day of the disease During the later stage of the infection the leucocyte count usually rose (Charts I and III) in 4 of the 12 cases reaching 10 000 to 13 700 without however a relative increase in the polymorphonuclear neutrophilic leucocytes

There was very little correlation in this group between the subjective symptoms and the continuation of fever and physical signs As the temperature fell coarse râles increased very noticeably *in numbers and* in many patients they first became noticeable during this period of defervescence when except for cough the patients were comfortable Rales and shadows in the x ray or both rarely disappeared before the tenth day of the disease and in eight patients the lungs were not clear to examina

were heard over some area of the chest In 2 patients a transient friction rub was heard In all the patients x rays disclosed shadows often extending from the roots of the lung towards the periphery or involving the peripheral portion of one lung in the mid or upper field The extent of these shadows was out of all proportion to what might be expected from the meagre physical signs In some instances the shadows appeared somewhat spotty in others they were diffuse and of varying density

C W 32 Sept 1939

DATE	2	3	4	5	6	7	8	9	10	11	12	13	14	15
DAY OF ILLNESS	4	5	6	7	8	9	10	11	12	13	14	15	16	17

TEMP

105 104 103 102 101 100 99 98 97

CHART II This patient male age 32 had a complicating chronic rheumatic heart disease and was severely ill Note lung involvement Temperature was normal on 15th day and convalescence was uninterrupted (From Longcope)

The left lung was involved in 9 cases the right alone in 3 and probably the right as well as the left in 2 In these 2 instances the shadows were first seen in the left lower lobe and later equivocal areas of density were noted in the right lower lobe with rales in these regions Shadows appeared in the left lower lobe in 5 patients in the left mid region or upper in 4 in the right middle in 1 and in the right upper in 2

The patients in this group rarely felt ill for more than two or three days and the most distressing symptom was usually the harassing rasping non productive cough None of them was cyanotic Blood cultures made in seven of the twelve patients gave no growth of bacteria

The course of the temperature always attracted attention (Charts I–

was involved A continued high fever a previous epistaxis a palpable spleen and low leucocyte count in one patient suggested at first that he was suffering from typhoid fever In a second patient the presence of small amounts of albumin and a few red blood cells and leucocytes in the urine drew attention at first to the urinary tract rather than to the

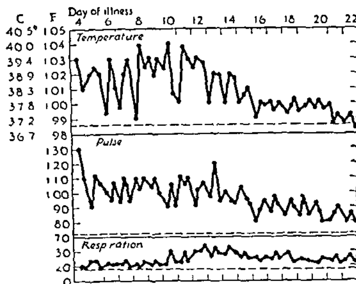


CHART V Severe infection of respiratory tract with nasopharyngotracheobronchopneumonia in male of 5 Leukocyte count at first 8 300 rose to 14 000 Dyspnea and cyanosis were marked about the second week of illness Convalescence was slow recovery complete (From Reimann and Havens)

lungs In a third patient who was found to have chronic rheumatic heart disease with mitral stenosis there was continuous expectoration of large amounts of bloody sputum The lower lobes were again the commonest seat of the lesion for one or the other or both were affected in 10 of the 11 patients In 7 patients more than one lobe was involved In 5 of the 7 patients two lobes were affected and in the other 2 three lobes

In all 11 patients there were during some stage of the illness physical signs indicating involvement of the lungs These were discovered in 5 patients by the third day of the disease Dullness suppression of breath sounds bronchovesicular breathing and a few râles were common Frank tubular breathing was comparatively rare As the disease progressed coarse râles became numerous and often persisted for many days or weeks after the temperature had fallen to normal The acute symptoms with

tion until between the fourteenth and twenty second day of disease Convalescence was uncomplicated quite rapid and recovery complete in this group

The character of the disease in this group of 12 patients simulates very closely the descriptions published in many of the reports that have been referred to previously Though these cases may represent the

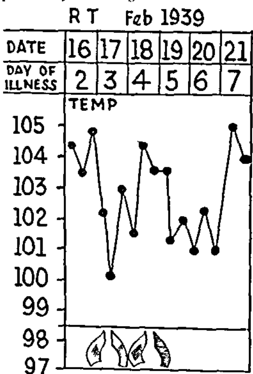


CHART IV This patient male age 38 died on 7th day of illness with very extensive lung involvement condition was complicated by chronic rheumatic heart disease He had watery diarrhea marked dyspnea deep cyanosis and delerium Autopsy showed extensive bronchopneumonia pulmonary edema mitral stenosis and small chromophobe adenoma of hypophysis (From Longcope[24])

commonest form of this particular variety of bronchopneumonia the disease does at times progress in a much more serious manner

This occurred in the 11 patients that form the second group In these patients the disease manifested its greater severity by an intensification and prolongation of the acute symptoms by the frequency of a secondary rise of temperature and a longer period of fever by the occasional appearance of cyanosis with more frequent occurrence of signs indicating disease of the lung and evidence in many cases from the physical signs as well as from the x ray that more than one lobe of the lung

was involved A continued high fever a previous epistaxis a palpable spleen and low leucocyte count in one patient suggested at first that he was suffering from typhoid fever In a second patient the presence of small amounts of albumin and a few red blood cells and leucocytes in the urine drew attention at first to the urinary tract rather than to the

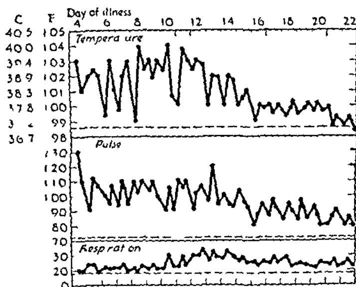


CHART V Severe infection of respiratory tract with nasopharyngeotracheobronchopneumonia in male of 25 Leukocyte count at first 8 000 rose to 14 000 Dyspnea and cyanosis were marked about the second week of illness Convalescence was slow recovery complete (From Reimann and Havens[1])

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fever lasted from 7 to 13 days in 7 patients and from 14 to 21 days in 4 patients The physical signs or shadows demonstrable by x ray persisted for 14 to 21 days in two patients for 22 to 27 days in 3 patients and from 28 to 80 days in 6 patients An otitis media occurred as a complication in 1 patient the remaining 10 patients recovered without complications

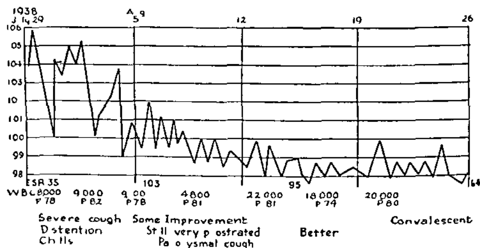


CHART VI This patient male age 29 had severe paroxysmal dry hacking cough and in first week was very ill Chart shows chief features of illness Note rising leucocyte count as temperature is falling Convalescence was slow recovery complete (From Kneeland and Smetana[23])

In the last group of 9 cases though the symptoms at onset did not differ in any remarkable way from those previously described the subsequent course assumed the character of an intense infection The cough was persistent the breathing sometimes of asthmatic type headache was intense sweating common and prostration severe As the disease progressed cyanosis became prominent and in some patients was so intense that it was not entirely relieved by oxygen therapy This was particularly true of one of the two fatal cases both of whom had chronic rheumatic heart disease In all of these patients there was a transient fall in temperature during the first week of the disease with a subsequent rise followed by a prolonged febrile period

During the course of the illness the pneumonic process spread from one part of the lung to another sometimes involving three or in one case four lobes in a patchy manner Some signs of solidification were common

in this group of patients for dullness and small areas of tubular breathing occurred in all cases There were apt to be few rales during the early stages but coarse often explosive râles appeared in great profusion in the latter part of the illness and during convalescence The duration of the acute febrile illness in the seven patients who recovered was protracted lasting in one patient 13 days in one patient 15 days in two 17 days in one 20 in one 23 and in one patient 25 days

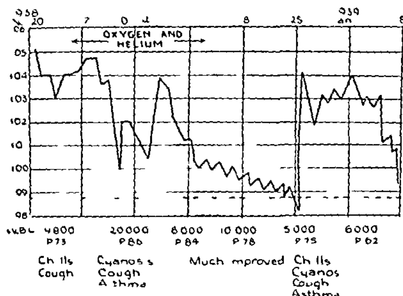


CHART VII This patient male age 30 had an acute illness of 7 weeks with an asthmatic type of dyspnea Leucocytosis developed during second and third week when patient was critically ill Patient had a relapse Chart shows chief features of illness Patient was hospitalized for 10 weeks and then made slow complete recovery (From Kneeland and Smetana[23])

The residual physical signs and the diminishing x ray shadows however persisted for a much longer time lasting for at least one to two months In one patient the disease was complicated by thrombosis first of the right femoral vein then of the left with subsequent infarctions of the lung Except in this patient there were no instances of pleurisy There was either a leucopenia or a leucocyte count within the limits of normal during the early stages of the disease in all of these patients with a subsequent moderate leucocytosis of 13 000 to 17 000 in 6 cases Recovery in 7 patients was complete without residual abnormalities in the lung

Clinical charts (Charts I–VIII) taken from the papers of Reimann and Havens[19] Kneeland and Smetana[23] and Longcope[4] illustrate well the course of the disease with varying types of fever usually falling gradually to normal except in fatal cases (Chart IV) Early in the disease there may be leucopenia but more often the white cell count is normal or slightly elevated later in the disease a polymorphonuclear leucocytosis to 12 000

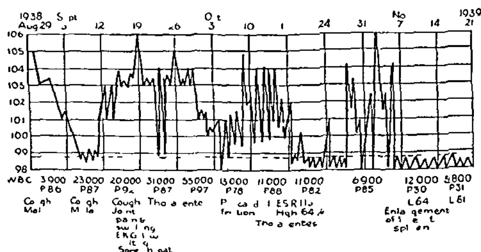


CHART VIII This patient female age 35 had a prolonged migratory bronchopneumonia with tendency to relapses an erratic leukocyte count and both pleuritis and pericarditis Chart shows chief features of illness After 12 weeks of illness slow recovery ensued (From Kneeland and Smetana[23])

to 18 000 is frequent persisting after the temperature is normal or even appearing only after temperature has returned almost to normal Sputum is sparse very rarely bloody not rusty containing relatively few bacteria of types common in the mouth with findings in some of fairly numerous pneumococci of higher types or hemolytic or viridans streptococci Leucocytes are infrequent until later in very sick patients but mononuclear cells may be numerous Blood cultures almost always have been negative a few have shown streptococcus viridans

Some patients develop acute pulmonary symptoms with intense cyanosis racking cough sometimes obstructive type of respiration in some there are the physical signs of acute pulmonary edema With this patients may show vasomotor circulatory collapse with cold sweat Others have the same circulatory collapse without cyanosis they are ashen gray cold with skin moist These are the phenomena we saw often during the

1918 epidemic of influenza when they contributed largely to the mortality of that disease

Cold hemagglutinins develop frequently during the course of the disease or during convalescence Although in no sense specific for this group of pneumonias, their occurrence in a greater frequency than in other infectious diseases is in itself suggestive that the pneumonitis of the patient had the etiology of the great majority of cases of non bacterial pneumonias i e an unidentified organism probably of viral type Agglutinins for streptococcus MG also appear in half or more of these patients

Complications

Complications are infrequent Of Longcope s patients[4] one had otitis media another thrombophlebitis in both legs with subsequent pulmonary infarction others had erythematous skin lesions In Kneeland and Smetana s[3] patients one had thrombophlebitis in the legs one had signs of encephalitis others had jaundice hematuria, migratory polyarthritis erythematous skin eruptions and fibrinous pericarditis they consider some of these part of the disease or possibly associated with the diffuse acute vascular lesions which they found in their one fatal case Reimann and Havens[19] noted encephalitis in 2 acute gastrointestinal disturbance with diarrhea in 4 jaundice like catarrhal jaundice in 3 maxillary sinusitis in Herpes labialis is infrequent as is pleurisy

Diagnosis

There is no single specific diagnostic finding in non bacterial pneumonias although as already described the appearance of cold hemagglutinins[3] in a patient with the following clinical characteristics is highly suggestive of the diagnosis of non bacterial pneumonia Actually there is very little doubt of the diagnosis when the following clinical features are observed These are onset with fairly high to high fever accompanied by a rasping persisting often paroxysmal cough with mucoid or mucopurulent sputum which unlike that of bacterial pneumonia contains no blood and smears from which show no pathogenic bacteria there is a paucity of physical signs except rales in contrast to the x ray evidence of areas of pulmonary consolidations the areas of pulmonary consolidation are strikingly migratory in character as followed in repeat x rays

PROGNOSIS

Prognosis for recovery has been excellent in reported cases, Longcope[31] had 3 fatalities in 43 patients Kneeland and Smetana[3] 1 in 52 cases, Reimann and Havens[29] none in 100 bed cases These were cases seen previous to the finding of an effective therapy Now with aureomycin deaths have become very infrequent and convalescence is of rather brief duration except in old people in whom all infections leave a quite lasting trail of disabilities the older the patient the longer the convalescence from infections and infectious diseases is a good rule to remember

PROPHYLAXIS AND TREATMENT

Avoidance of direct contact with patients having this disease including wearing of gauze masks by nurses doctors and others who must come close to them is the only available prophylaxis

Non bacterial pneumonia should have the same general measures of treatment as advised for bacterial pneumonia including bed rest, nursing care and a simple largely liquid and semisolid diet (see first paragraphs of Treatment in the chapter Acute Lobar (Pneumococcal) Pneumonia Chapt XXVII Vol IV of Oxford Medicine) Aureomycin[44 to 51] has been found to be the most effective drug in non bacterial pneumonia causing in a large majority of the patients a fall in temperature to normal usually in 12 to 24 hours after this antibiotic therapy has been begun, with a corresponding improvement in symptoms If aureomycin is stopped soon after the temperature reaches normal, there is a tendency for relapse to occur so it should be continued for several more days If relapse does occur repetition of treatment with aureomycin usually gives again a prompt drop in temperature and clinical improvement For these patients aureomycin with very few exceptions is to be given by mouth, the dosage usually should be 1 gm (gr 15) given at 6 or 4 hour intervals a total of 4 to 6 gm (gr 60 to 90) each 24 hours until the temperature reaches normal and thereafter 1 gm (gr 15) twice a day for several more days Nausea often and vomiting and/or diarrhea not infrequently follow the taking of aureomycin These can be lessened by the taking of milk aluminum hydroxide gel or phenobarbital Sometimes when these symptoms are marked it is better to reduce the unit dose at least temporarily from 1 gm (gr 15) to 0 5 gm

(gr 7½) this dosage often is effective and larger dosage is not needed

In an occasional very ill patient it seems advisable to give aureomycin intravenously For this it can be dissolved in 1 leucine in 5 ml of this diluent, containing 131 mgm of leucine 100 mgm (gr 15) of aureomycin can be dissolved This solution can be injected intravenously at a very slow rate or it can be added to a solution of normal saline with or without 5 per cent dextrose By this means 4 to 5 gm (gr 60 to 75) of aureomycin may be given at 12 hour intervals

Aureomycin has the advantage of effectiveness not only in those patients with non bacterial pneumonia of probable but still definitely undetermined virus etiology which make up the largest proportion of these cases but also in those in whom the etiological agent is a ricketsial or viral organism such as causes psittacosis ornithosis Q fever etc Aureomycin also is effective against a variety of bacteria which can cause secondary pneumonia and various complications In a way aureomycin is a happy shot gun form of therapy for pneumonitis of various causes

Cough which was such an annoying symptom usually is not troublesome when aureomycin is used If it does occur it should be treated with mentholated throat lozenges medicated steam vapors a snugly fitting binder over the lower ribs codeine and oxygen inhalation

Circulatory collapse if it does occur should be managed as described in the chapter on Lobar Pneumonia already referred to

Prognosis

Prognosis for recovery has been excellent in reported cases Longcope[11] had 3 fatalities in 43 patients, Kneeland and Smetana[3] 1 in 52 cases Reimann and Havens[19] none in 100 bed cases These were cases seen previous to the finding of an effective therapy Now with aureomycin deaths have become very infrequent and convalescence is of rather brief duration except in old people in whom all infections leave a quite lasting trail of disabilities the older the patient the longer the convalescence from infections and infectious diseases is a good rule to remember

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CHAPTER XXXIII

ACUTE LOBAR (PNEUMOCOCCAL) PNEUMONIA

By ERNEST E. IRONS

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pneumococcal immunity including the relations of changes in the blood to the clinical course of the disease and methods devised with a view to controlling the spread of pneumonia and to its cure failed to take into account differences in types of pneumococci and consequently the pioneer work in this field has a relatively limited value in the solving of present problems Many of the discordant results and failures by one worker to confirm the findings of another are seen now to have been due to the assumption that all pneumococci belonged to a single homogeneous group Other seemingly contradictory observations such as recognition of the contagiousness of pneumonia and the finding of pneumococci in the mouths of 50 per cent of normal people most of whom however remain well are now explainable by the determination of virulent and relatively avirulent types of organisms

On the assumption that all pneumococci are alike the occurrence of a second attack of pneumonia formerly was taken as evidence that one attack of pneumonia predisposes to another whereas there is evidence that recovery from pneumonia due to one type of pneumococcus results in at least a temporary immunity to that type but not necessarily to other types one of which may give rise to the second attack The relation of the well known predisposing causes of pneumonia chilling exposure fatigue and trauma on the one hand and the spread of virulent pneumococci by contact with those ill or with carriers of virulent organisms on the other to endemic and to epidemic lobar pneumonia becomes clearer when the facts in a given case are considered with reference to the types of infecting pneumococci and is bringing about a very considerable reduction in mortality of these diseases

Still more important the determination of types of pneumococci has made possible the making of type specific sera which together with the newer chemotherapeutic agents have revolutionized the treatment of lobar pneumonia and pneumococcic infections

The Pneumococcus

E Klebs in 1875 found in fluids from the lung of fatal human pneumonia non motile monads sometimes linked in large numbers and probably was the first to see the pneumococcus In 1881 Pasteur and some three months later Sternberg published reports of animal inoculation and isolation of an organism now known as the pneumococcus During the following four years the labors of many men including Friedlander and Fraenkel established the etiological relation of the pneumococcus to lobar pneumonia

Introduction

Acute lobar pneumonia may be defined as an acute infectious disease characterized clinically by a toxemia with fever which often terminates by crisis and pathologically by a uniformly diffuse exudative inflammation of continuous portions of one or more lobes of the lung The cause is usually the *Diplococcus pneumoniæ* In the typical case with sudden onset chill fever pleuritic pain rapid respiration suppressed and later bronchial breathing crepitant râles dulness rusty tenacious sputum and critical drop in temperature after a few days illness no difficulty is met in establishing the diagnosis of acute lobar pneumonia

In other cases of pneumococcal pneumonia the early symptoms and signs are less distinctive but the subsequent findings and course leave little doubt as to the nature of the illness Infections of the lung by organisms other than the pneumococcus exceptionally may give rise to a clinical picture resembling pneumococcal lobar pneumonia and the post mortem examination may even reveal consolidation of lobar distribution but in general it may be said that the pneumococcus is the cause of acute lobar pneumonia The pneumococcus may be found also in bronchopneumonia and in respiratory diseases following infections such as influenza and measles as well as in infections of the upper respiratory tract sinuses and ears without clinical involvement of the lungs Other organisms such as the bacillus of Friedlander streptococci staphylococci and the bacillus of Pfeiffer have been found with the pneumococcus as mixed infections in cases of pneumonia In some instances these organisms may in the absence of the pneumococcus give rise to pneumonia of lobar distribution but usually the course of the illness is atypical and is characterized by bronchopneumonic distribution

The most important development in the past three decades in the study of pneumonia was the demonstration that the members of the pneumococcus group while in general similar in their cultural characteristics differ widely immunologically and in their invasive power for man and animals This discovery led to the recognition of a number of types of pneumococci whose reactions appear to be fixed and may be correlated with their pathogenic power and to some extent with the clinical manifestations of the disease in man Prior to 1910 practically all studies in

Pneumococcal Immunity

The study of immunity to pneumococcal infection dates from the experiments of Fraenkel who showed that rabbits which had survived a subcutaneous inoculation of virulent pneumococci were able to withstand a subsequent and otherwise fatal dose of pneumococci. In 1891 several workers, notably G. and F. Klemperer, showed that immune serum when injected into normal animals would protect against fatal infection by pneumococci. Immune sera possess a number of properties as evidenced by the agglutination of pneumococci, the precipitation of filtrates of cultures, the opsonification of pneumococci whereby the organisms are rendered susceptible to phagocytosis by leukocytes, and also the power to protect animals against infection by pneumococci. This latter quality has been attributed in part to agglutinins and opsonins and in part possibly to other reactions including that of the neutralization of products of pneumococcal growth within the body. Agglutinins, opsonins and the protective action of sera have been found most serviceable in the study of the changes which take place in the animal body in response to pneumococcal invasion. Much of the earlier work on pneumococcal immunity gave indecisive and often contradictory results until it was found that culturally similar pneumococci differ widely serologically. Eyre and Washbourn were among the first to recognize that strains of pneumococci differ from each other and that immune serum which affords protection against some strains will fail against others. Gradually the importance of distinguishing the several types of pneumococci was recognized, largely through the labors of Neufeld, Lister of South Africa and of Cole and his associates at the Rockefeller Institute.

Early in the study of pneumococcal infections it was noted that sterile filtered inflammatory exudates contained substances which influenced the course of infection and favored the invasion of the body by the pneumococci. Bail called these aggressins. Rosenow, studying the reaction of leukocytes in the presence of virulent and avirulent pneumococci, noted that the former resisted phagocytosis but that by repeated washings in salt solution they became phagocytable. He called the hypothetical substance which was thought to be thus removed virulin. Wolf determined the absence of pneumococcal opsonin in pneumococcal exudates. Cole found that not only do pneumonic exudates contain no agglutinins or protective bodies, but that portions of the exudate actually neutralize or render inactive the agglutinins and protective bodies in immune sera. He further showed that similar inhibiting substances are present in the serum of animals in which severe pneumococcal septicemia has been produced.

The *Diplococcus pneumoniæ* is an oval lance shaped coccus growing in pairs placed end to end or singly, or sometimes in chains It is non motile Gram positive does not form spores and is soluble in bile In animal fluids and in cultures containing such fluids the pneumococcus is surrounded by a capsule which envelops single organisms or pairs This capsule is a distinctive morphologic feature of the organism Chemical and immunological studies of the capsular material have shown that in it reside the qualities which determine the immunological differences between the several types of pneumococci The swelling of the capsule (*Quellung reaction* of Neufeld) when pneumococci are exposed to the action of the corresponding type antiserum has greatly facilitated the identification of the types of pneumococci in the sputum and makes possible the early administration of suitable antiserum

Early studies of pneumococcal types resulted in the establishment of three so called fixed types types I II and III (Dochez and Gillespie) Pneumococci not conforming to these three types were placed in type or group IV Later work resulted in the separation of group IV into some 29 types so that there were recognized some 30 types (Cooper) With still further systematic typing of pneumococci strains have been found which do not conform to any of the above numbered types and at the present time there are upwards of forty types distinguishable immunologically Somewhat over half of the cases of lobar pneumonia are caused by the first three types About 30 per cent more are caused by types IV V VI VII and VIII Cecil found the following distribution of pneumococcal types in 5 779 cases of lobar pneumonia (Table I)

TABLE I

Type	*Cases*	*Per Cent*
I	1 642	28 4
II	704	12 2
III	691	11 9
IV	275	4 8
V	409	7 1
VI	95	1 6
VII	358	6 2
VIII	397	6 9
IX–XXXII	1 208	20 9

The higher numerical types so far have been found more frequently in children It should be noted also that the relative incidence of the several types varies from year to year and in different communities

selves in the blood fixed a portion of the immune substances in the serum but in some instances the blood was sterile at the time when disappearance of immune substances was observed

It would appear that no matter what may be the relative importance of the several supposed protective mechanisms in pneumonia whether protection is accomplished by phagocytosis in the presence of immune bodies or by other antipneumococcal agencies contained in the immune serum there must be supplied a sufficient amount of immune serum for these purposes and enough more to take care of any soluble toxic material which has accumulated in the blood and tissues

Recovery from pneumonia is coincident with the presence of immune substances in the blood which appear about the time of crisis The duration of immunity conferred by the infection may be short and from experimental and clinical evidence it is for the most part effective only against pneumococci of the same type as that causing the infection Cecil and Blake found that in monkeys an attack of type I pneumonia protected against a second attack of the same type but little or not at all against infection by type II

The injection into patients early in their illness of adequate amounts of antiserum corresponding to the type of infecting pneumococcus causes clinical improvement limits the spread of infection shortens the course of the illness and reduces the case fatality rate The duration of evidences of immunity produced by immunization of animals by injection of pneumococci varies from a few weeks to a year In man the demonstrable antibody response to active immunization has been shown to persist for from three to fourteen months Following specific serum treatment the duration of evidence of immunity in man is shorter than after spontaneous recovery and may persist for only a few days or weeks In general pneumococcal immunity seems to be of shorter duration in man than is that of certain other infectious diseases

The Francis test is as follows

Francis Test

The test is performed by the intradermal injection of 0 1 c c of a 1-10 000 solution of polysaccharide in normal salt solution using the volar surface of the forearm a control injection of 0 1 c c normal salt solution is made a few centimeters from that of the polysaccharide In a positive test a wheal appears within 15 to 30 minutes surrounded by an area of erythema The reaction is believed to be due to a local union of polysaccharide and antibody in the skin and thus indicates that an

The formation of specific substances by the pneumococcus has been studied also by means of the precipitin reaction Neufeld found that cultures in which the pneumococcus had been dissolved by the addition of bile contained a substance precipitable by immune rabbit serum and Wadsworth obtained similar results using salt solution extracts Dochez and Avery demonstrated a specifically reacting substance of bacterial origin in cell free fluids from young cultures of pneumococci and a similar substance in the blood and urine of infected rabbits and of patients ill with pneumococcal pneumonia

More recent immunologic studies indicate that the substance of the capsule of the pneumococcus contains a polysaccharide which differs in character in different types of pneumococci and is believed to confer on the several types of pneumococci their type specific qualities as well as to constitute an important source of virulence Pneumococcal capsular polysaccharides appear to be antagonistic to pneumococcal anti bodies produced in the immunized animal or in the human subject recovering from pneumonia When present in sufficient amount the poly saccharides neutralize or inhibit the action of the protective antibodies The intradermal injection of type specific polysaccharide in a patient recovering from pneumonia or to whom an adequate dose of antiserum has been administered results in a positive local reaction with wheal and surrounding erythema This reaction is absent at the beginning of the pneumonia and after convalescence and has been suggested by Francis as a means of gauging the adequacy of antiserum treatment Almost all patients with type I pneumonia react with type I polysaccharide about one half of type II pneumonias react with type II polysaccharide and a smaller proportion of type III cases show the reaction There occur about 10 per cent of non specific reactions in the Francis test and with less pure products a larger number

On the other hand products of the bodies of pneumococcal cells so matic C substance give cutaneous reactions early in the disease which disappear with convalescence persist longer where complications occur and are not type specific

The determination of the presence of these substances in the blood and exudates of the subjects of pneumococcal infection is of interest not alone as some indication of the mechanism of pneumococcal invasion but because of its bearing on methods of specific therapy Cole found that when immune serum is administered to animals or to patients severely infected with pneumococci the immune bodies introduced in the serum become effective only when sufficient serum has been administered to neutralize these substances completely He noted that pneumococci them

Social conditions and occupation seem in general to be more important than climate The highest incidence of pneumonia in temperate zones is in the winter and early spring Sudden changes in temperature favor an increase in pneumonia The incidence of pneumonia is greatest among the very young and the old and lowest in the age period 15 to 30 The morbidity and mortality are greater in males than in females The negro is more susceptible to pneumonia than the white and this susceptibility is accentuated when the negro moves from a warm to a cold climate

While acute lobar pneumonia generally is regarded as an endemic disease it has long been recognized that groups of cases in houses schools prisons or other situations where several persons are in close contact frequently occur and if the number of persons infected is sufficiently great the epidemic character of the outbreak becomes evident Large epidemics of pneumonia have occurred notably at Panama during the building of the canal and in the Rand Mines in South Africa In both of these regions the highest incidence of disease was among imported colored laborers from the West Indies at Panama and from Central Africa at the Rand Mines The susceptibility to pneumonia of the African natives was found to be greater among those coming from Central Africa than among those from the East Coast The importance in the production of pneumonia of close association in barracks of men brought from regions where respiratory infections were less common was noted among laborers at Panama and emphasized by the experience in the camps in the United States during the World War I Soldiers from the country districts suffered more severely from respiratory diseases including pneumonia than did those from large cities and in both classes the incidence of pneumonia was higher than in the same age groups in civil life Overcrowding in tents or barracks further increased the frequency of respiratory infection of the recruits

The difference between the susceptibility of new recruits to disease as compared with seasoned soldiers was evident in the greater incidence of epidemic respiratory infections among the former The same difference has been noted between newly arrived and older laborers in the Rand Mines The increase of resistance to disease after a few months service known as long as there have been armies is no doubt in part explained by the adjustment of the new soldier to new conditions of life whereby he learns to take better care of himself and by a gradual increase in his immunity through repeated slight respiratory infections derived from his fellows

Early bacteriological studies of the mouths and throats of normal persons in whom pneumococci were found in perhaps 50 per cent threw

excess of type specific antibodies is now present in the blood and that, therefore no more antiserum is required A preliminary test made before the patient has received serum should be negative so that a later positive test shall be significant The polysaccharide should contain no C fraction of the pneumococcus (derived from the pneumococcal cell body) if false positives are to be avoided The type specific polysaccharide corresponding to the type of pneumococcal infection in the patient is used in the test Type specific capsular polysaccharides of pneumococci of types I to VIII and XIV free of C fraction were employed by Wood who found the test of value in determining when adequate serum dosage had been given It was of assistance also in determining whether recurrence or continuation of fever was due to uncontrolled pneumococcal infection in the lung or to complications such as empyema or extrapulmonary lesions In Wood s series of 57 patients 5 gave positive tests before serum was given thus making the test of no value in these patients

Epidemiology

Lobar pneumonia is endemic and often epidemic in all parts of the world from the arctic to the tropics Attempts to estimate the general trend of mortality rates over several decades are impeded by lack of uniform terminology in vital statistics by confusion in use of the terms pneumonia lobar pneumonia bronchopneumonia etc and by changes of custom in the use of these terms from decade to decade In the United States registration area 1920–29 there were 1 006 869 deaths from pneumonia (all forms) of which 525 465 (4 3 per cent of all deaths) were from lobar pneumonia In Massachusetts (1920–1929) deaths per 100 000 population varied from 163 to 95 (all forms) while the rate for lobar pneumonia and undefined pneumonia together varied from 74 to 46 During this decade pneumonia oscillated between second and fourth as the most important cause of death (Heffron)

In the United States and Canada mortality rates from pneumonia are higher in some cities and states than in others Two pneumonia belts have been pointed out in studies by the Metropolitan Life Insurance Company One of these extends from Quebec down the Atlantic Coast to include Georgia and inland to include Tennessee and Missouri The second region of high pneumonia rates includes Colorado New Mexico Arizona and Nevada Thus far no single common factor in climate latitude or race has appeared The mortality rate and probably the morbidity rate is higher in urban than in rural communities A study of deaths from pneumonia of all forms from 1920 to 1932 in the ten original registration states indicates a slightly downward trend

resistant to infection or whose resistance is accidentally lowered by external factors

The assumption which appears amply justified on clinical and epidemiologic grounds that persons differ widely in their individual resistance to pneumococcal infections has received experimental support from the work of Clough who tested the protective power of the serum of 25 normal persons against virulent pneumococci Of 18 serums tested with type I pneumococcus 4 showed protective power of 18 serums tested with type II 8 protected of 19 tested with type III 8 protected In some instances the protective power was as great as that seen in persons convalescent from pneumonia or in vaccinated persons In none of these serums however was it possible to demonstrate agglutinins precipitins or bacteriolysins nor could a summation of protective power be demonstrated when a highly protective normal serum was combined with an artificial immune serum

While there is still much to be learned of the relation of types of pneumococci to the incidence of pneumonia the knowledge already gained makes clear the contagious element in the spread of pneumonia

In the recurrences of pneumonia the determination of the type of pneumococcus has shown in some instances that the organism of the second attack is different from that of the first In one case cited by Stillman a patient convalescent from a type I pneumonia visited his brother who was ill with a type II pneumonia and two days later himself became ill with a type II infection In the absence of methods of differentiation of pneumococci into types this observation formerly would have been regarded as an instance of predisposition produced by one attack to a subsequent attack of pneumonia whereas the two attacks were due to distinct infections the first of which produced no immunity to the other

Cecil and Blake obtained direct experimental evidence that one attack of type I pneumonia produces in monkeys immunity to subsequent infection by the homologous type and a slight degree of cross immunity to other fixed types Monkeys convalescent from group IV pneumonia however showed no evidence of immunity against a second infection by type I pneumococcus

As the means of spread of pneumonia become more widely understood it seems likely that greater emphasis will be laid on the epidemic in contrast to the endemic features of the disease Systematic typing of pneumococci in the military camps during the war (1917–1919) showed striking differences in the distribution of types of pneumococcus during a given period in localities in which climatic conditions were fairly comparable

but little light on the problem of epidemiology of pneumonia and tended rather to overemphasize the role of individual contributory factors such as exposure chilling lack of food or fatigue It is now known that while pneumococci frequently occur in the mouths of healthy persons as a rule they do not belong to the more common disease producing types Persons in close contact with those ill with pneumonia however sometimes harbor the more pathogenic types and usually the same type as that found in the sick to whom they have been exposed Stillman examined 297 persons in whom no history of contact with an acute or recent case of lobar pneumonia could be obtained From the mouth secretions of 116 pneumococci were isolated among which type I occurred once and type II not at all Subtypes IIa IIb and IIx were found 22 times (18 2 per cent) type III (*pneumococcus mucosus*) was found 34 times (28 1 per cent) and group IV 64 times (52 9 per cent) On the other hand in 454 cases of pneumonia types I and II were present in 284 instances (62 6 per cent) The dominance of these two types of organisms in pneumonia was in striking contrast with their relative absence in the mouths of normal persons

Healthy contacts with type I cases have been found to harbor type I pneumococci in from 4 5 per cent to 24 2 per cent by various observers an average in 870 cases of 10 0 per cent similarly in contacts with type II cases type II pneumococci were found in 13 0 per cent and with type III cases type III pneumococci in 18 0 per cent (Heffron) The incidence of pneumococci of homologous type seems in general to be higher among family contacts than among contacts of hospital personnel

The duration of the carrier state varies greatly Healthy non contacts may harbor pneumococci intermittently or in some cases persistently for many months pneumococci acquired by contact disappear from the throats usually after two or three weeks In patients convalescent from pneumonia pneumococci disappear from the throats in a few days or sometimes may persist for weeks or months Types I and II seem to persist longer than members of the higher numerical types The persistence of pneumococci in carriers frequently seems related to coincident chronic upper respiratory infections

The presence of virulent pneumococci in the mouths of healthy persons does not necessarily result in pneumonia but when such persons are susceptible to pneumococcus invasion or in case they are subjected at the same time to unusual exposure chilling or other depressant conditions such as minor respiratory infections pneumonia may result The production of pneumonia by those strains of pneumococci regarded as less virulent is probably to be explained by their occurrence in persons less

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experiments in animals under ether anesthesia or after chilling have produced experimental pneumonia Intravenous injection of pneumococci produces pneumococcal sepsis but not lobar pneumonia

*Blake and Cecil produced lobar pneumonia in monkeys by the injec*tion of pneumococci through a sterile needle introduced into the lumen of the trachea below the larynx The pneumonia produced resembled clinically and pathologically that in man In monkeys so inoculated pneumococci sometimes were found in the blood within six to twenty four hours and before fever or clinical evidence of pneumonia had appeared In contrast with the regularity with which pneumonia resulted from intratracheal injection was the failure of pneumonia to develop where pneumococci were sprayed into the nose and throat of monkeys In some animals virulent pneumococci persisted as long as a month in the secretions of the mouth without any signs of illness

Robertson found that when pneumococci were forcibly sprayed deep into the bronchial tree of the dog pneumonia usually failed to develop but if much smaller numbers of pneumococci were suspended in a viscous starch broth paste and then introduced into the bronchi pneumonia regularly resulted Whether the pneumococci were merely protected from mechanical action of cilia cough and bronchial contractions or whether the starch paste caused local tissue injury could not be determined Possibly both factors played a part Acute colds frequently precede pneumonia and thus may injure lung tissue sufficiently to allow pneumococci if present to establish a foothold The reduction of temperature in the dog by the administration of morphine also facilitated the production of experimental pneumonia The presence of a cold with perhaps an accompanying bronchial irritation and secretion of mucus with added chilling and fatigue may well prepare the lung for the implantation of pneumococci inhaled with droplets suspended in the air Robertson has described a case of type I lobar pneumonia in a laboratory worker in whom the disease *followed possible exposure to a droplet spray contain*ing type I pneumococcus A few months later type II pneumonia occurred in the same worker after possible exposure to type II droplet infection

Pathology

The outstanding features of the morbid anatomy of lobar pneumonia are the classical stages of engorgement red and gray hepatization and resolution of the affected regions of the lung the uniform continuous (lobar) distribution of the inflammation and the marked production of

At Camp Grant Rockford Illinois up to March 1 1918 type III pneumococcus had been isolated in 8 cases but not at all at Camp Taylor Louisville Kentucky Type I pneumococcus was found in 25 instances at Camp Sherman Columbus Ohio 28 times at Camp Taylor and 7 times at Camp Grant while at Camp Custer Battle Creek Michigan no cases of type I were encountered until April 1918 With the arrival at Camp Custer in April of 2 000 Alabama negro troops type I pneumonias began to appear and 17 cases of type I pneumonia developed in two barracks of these troops and 8 other cases in the camp

Studies of type incidence in hospitals show marked changes in proportions of the several types from year to year

The well known increase of pneumonia during winter and spring months and its variation in prevalence from year to year while no doubt dependent on climatic factors affecting both conditions of living of the population and of the viability of the pneumococcus appear to be affected also to a degree perhaps greater than hitherto has been supposed by epidemic factors arising from close contact

Predisposing Factors

Epidemic seasonal and other general factors influence the incidence of lobar pneumonia in communities but in addition its occurrence in the individual is determined by other more personal conditions Susceptibility to pneumonia is greater in young than in older children and increases in adult life with each decennium Men are affected more often than women probably by reason of greater occupational exposure to chilling and to accidental contacts with other infected persons The close and frequent contacts of urban life with over crowding overheating and unsanitary conditions of residence and poor and insufficient food result in the high incidence as well as the high mortality of pneumonia in cities compared to rural communities Sudden chilling exposure to wet and cold fatigue lack of food and the habitual use of alcohol contribute to personal susceptibility and frequently determine the onset of pneumonia Trauma to the chest may be followed by pneumonia

The Mechanism of Infection

Experimental and clinical evidence indicates that the organisms producing pneumonia in man enter through the air passages Early attempts to produce pneumococcal infection in animals by spraying pneumococci into the upper air passages usually failed but more recently inhalation

experiments in animals under ether anæsthesia or after chilling have produced experimental pneumonia. Intravenous injection of pneumococci produces pneumococcal sepsis but not lobar pneumonia.

Blake and Cecil produced lobar pneumonia in monkeys by the injection of pneumococci through a sterile needle introduced into the lumen of the trachea below the larynx. The pneumonia produced resembled clinically and pathologically that in man. In monkeys so inoculated pneumococci sometimes were found in the blood within six to twenty-four hours and before fever or clinical evidence of pneumonia had appeared. In contrast with the regularity with which pneumonia resulted from intratracheal injection was the failure of pneumonia to develop where pneumococci were sprayed into the nose and throat of monkeys. In some animals virulent pneumococci persisted as long as a month in the secretions of the mouth without any signs of illness.

Robertson found that when pneumococci were forcibly sprayed deep into the bronchial tree of the dog, pneumonia usually failed to develop, but if much smaller numbers of pneumococci were suspended in a viscous starch broth paste and then introduced into the bronchi, pneumonia regularly resulted. Whether the pneumococci were merely protected from mechanical action of cilia, cough and bronchial contractions, or whether the starch paste caused local tissue injury could not be determined. Possibly both factors played a part. Acute colds frequently precede pneumonia and thus may injure lung tissue sufficiently to allow pneumococci, if present, to establish a foothold. The reduction of temperature in the dog by the administration of morphine also facilitated the production of experimental pneumonia. The presence of a cold with perhaps an accompanying bronchial irritation and secretion of mucus with added chilling and fatigue may well prepare the lung for the implantation of pneumococci inhaled with droplets suspended in the air. Robertson has described a case of type I lobar pneumonia in a laboratory worker in whom the disease followed possible exposure to a droplet spray containing type I pneumococcus. A few months later type II pneumonia occurred in the same worker after possible exposure to type II droplet infection.

Pathology

The outstanding features of the morbid anatomy of lobar pneumonia are the classical stages of engorgement, red and gray hepatization and resolution of the affected regions of the lung, the uniform continuous (lobar) distribution of the inflammation and the marked production of

fibrin as evidenced by viscid sputum shaggy pleural exudates rapidity and extensiveness of post mortem clotting of the blood and by the fibrinous alveolar plugs in surfaces made by cutting the consolidated lobe The inflammation is characterized in succession by exudation of edema fluid and erythrocytes into the alveolar lumens by obliteration of air spaces from consolidation of the exudate and finally by removal of the exudate by liquefaction phagocytizing macrophages and absorption or by expulsion through the bronchi

In the initial stage of *engorgement* the affected portion of the lung is red to purple boggy enlarged and less crepitant than normal and bloody serum escapes freely from the surfaces made by section The capillaries are dilated and engorged with erythrocytes and the lumens of the alveoli are filled with fluid exudate mixed with erythrocytes and a few polynuclear leucocytes With the increase in exudate the appearance of the lung shades into the stage described as *red hepatization* in which the lung is red friable and firm like liver and the pleura covered with a thin layer of fibrin The cut surface is red to brown dry and granular and turbid red serum exudes from the alveoli and bronchioles when the surface is scraped with the edge of a knife The exudate now contains more fibrin erythrocytes and polymorphonuclear leucocytes some of which contain cocci This stage merges into that of *gray hepatization* The leucocytes become more abundant and the red cells decrease Towards the end of the gray stage the surface made by sectioning is more moist with purulent fluid and the granules less distinct Microscopically macrophages derived from the thickened alveolar walls appear free in the alveoli and actively phagocytize red cells polynuclear cells and pneumococci digesting them rapidly Fibrin is dissolved and the alveolar exudate is thinned The removal of the exudate proceeds stage of *resolution* largely by liquefaction and absorption of the formed exudate and by its expulsion through the bronchi The alveolar epithelium regenerates and the alveoli become again air containing The macrophages attached to the alveolar walls persist for some days or weeks

Robertson has described the pneumonic process in dogs following the injection of a small amount of pneumococcus culture suspended in a starch broth paste through a radio opaque catheter into a terminal bronchus Within one or two hours the pneumococci are still demonstrable in the starch filled alveoli and the inflammatory reaction consisting of quantities of fluid exudate red cells and polymorphonuclear leucocytes within the alveoli has begun The lesion at first is irregular situated along neighboring small bronchi and has the appearance of bronchopneumonia Soon however the small areas of inflammation coalesce and form

a continuous region of cellular infiltration characteristic of lobar pneumonia The site of the early lesion may be anywhere in the lung and spreads in any direction

The most striking feature of the early lesion is the profuse edema within the alveoli stimulated by products of the growing pneumococci Pneumococci multiply rapidly in this fluid and are carried into fresh portions of adjacent lung by the fluid advancing through the bronchioles and between the cells of the alveolar walls Phagocytosis of pneumococci by polymorphonuclear leucocytes begins early but of necessity lags behind the zone of advancing edema fluid As the process of consolidation continues the alveoli become filled with cells and fibrin The contained leucocytes lose their phagocytic effectiveness in two or three days but this function is now taken over by the macrophages derived from mononuclear cells of the blood and from the alveolar walls The macrophages are the active cellular agents concerned in resolution Robertson was able to demonstrate in human material that the stages resembled in every respect the changes observed in the dog

By reason of the development of the pneumonic lesions through successive stages it is unusual to find the entire lesion in any one stage The lesion may progress at different rates in different parts of the lung or a new lesion may appear in another lobe

Disturbances in the normal course of resolution may occur *In delayed resolution* autolysis of the exudate is hindered possibly by failure of the macrophage reaction Circulation of blood through the affected lung while impaired usually is sufficient to protect the tissue cells from the action of lytic ferments but sometimes the liquefying process involves both the exudate and the alveolar walls with the formation of *abscess* Rarely resolution does not occur the exudate in the alveoli and bronchioles being organized by granulation tissue and later by scar tissue so that the lobe becomes a gray contracted homogeneous mass This is known as *carnification* or *chronic fibrous* or *unresolved pneumonia* While it may follow lobar pneumonia it results frequently from other causes

Any lobe or any combination of lobes may be affected The right upper lobe is involved somewhat more frequently than are the others The gross changes at necropsy are characteristic The affected lung is large weighing from 1 200 to 2 000 grams (normal 300 grams) The pneumonic lesion may lie wholly within the lobe but usually extends to the periphery The visceral pleura is translucent to opaque some of its capillaries engorged with blood and it is covered by fibrin which may be barely visible to the naked eye or may cover the pleura in a shaggy layer several millimeters thick There is a turbid serous fluid mixed with fibrin

in the pleural cavities Fibrinous pleuritis is frequent in 94 6 per cent of 155 necropsies in which the condition of the pleura was noted (Fabyan) In the lumens of the bronchi there is turbid thin frothy fluid and the lining is red from engorged capillaries The tracheobronchial lymph nodes are enlarged and moist In the uninvolved portions of the lungs frequently there is passive hyperemia and edema

Empyema often interlobar or localized may be found when death occurs late in lobar pneumonia It was found in 14 7 per cent of 400 necropsies at the Boston City Hospital (Berry) Mediastinitis is found occasionally

The right cardiac chambers are distended with clotted blood which often extends in a continuous clot into the small branches of the pulmonary artery There is frequently a marked degree of cloudy swelling of the myocardium but other alterations are uncommon Acute fibrinous or fibrinopurulent pericarditis usually overlooked during life often is present (24 per cent Stone 12 6 per cent Cowan) It may result from the bacteremia or it may be due to direct or lymphatic extension from the pleura The early alterations of thrombo ulcerative endocarditis are at times encountered at necropsy A history of preceding pneumonia is frequent in instances of advanced thrombo ulcerative endocarditis especially of the aortic cusps

Acute fibrino purulent meningitis may be an early cause of death in overwhelming pneumococcal infections or later in persisting sepsis or consecutive to endocarditis Purulent arthritis is found occasionally (0 2 per cent Warr and Alperin) Peritonitis has been noted in 0 16 per cent to 3 0 per cent of necropsies by various observers Cellulitis subcutaneous abscesses and furunculosis (usually not pneumococcal) occur

Moderate enlargement of the spleen cloudy swelling of the liver and kidneys and dilatation of the large and small bowel (ileus) probably are effects of toxemia and fever Similar changes probably of toxic origin have been noted on microscopic examination of the adrenals and pancreas The pneumococcus often is recovered in cultures from the lung blood spleen and exudates

Onset and Physical Signs

The sudden onset with chill fever pain cough rusty sputum rapid respiration and physical signs of consolidation in one or more lobes of the lung make the picture of the typical case of lobar pneumonia characteristic and hardly to be confused with any other disease The incubation period is short In experimental pneumonia in monkeys the symptoms appeared in 8 to 12 hours following intratracheal injection (Cecil) In

Stillman's case pneumonia developed two days after contact with another type II pneumonia. The close time relation between chilling and physical exposure and the onset of pneumonia is of common observation. In about half the cases infections of the nose and throat or cough and bronchitis giving rise usually to minor symptoms or moderate malaise have preceded the pneumonia. The relative prominence of the early symptoms of pneumonia, fever, chill, cough, expectoration, pain, dyspnœa, is determined by the severity of the infection and other factors, such as preexisting respiratory infections or the location of the early lesion in the lung. The rapid increase of fever gives rise to the initial chill, frequently the first symptom of illness. Early pleural involvement produces pain, which sometimes is the first symptom noted by the patient.

The symptoms at onset may seem to be only those of an accentuation of previous mild cold or bronchitis, or they may be those of an overwhelming general infection in a person a few hours before in perfect health, with fever, headache, vomiting and profound prostration and with nothing pointing specially to the pneumonia which will become evident shortly. While the absence of one or more of the early symptoms of pneumonia may give rise to uncertainty of diagnosis during the first hours of illness, the nature of the disease usually soon becomes clear. The fever remains high (103 to 104 F.) with only slight remissions, the face is flushed, tongue heavily coated, respirations rapid and often painful. The cough, dry at first, soon is productive of blood-stained and later rusty, sticky sputum. On examination of the chest on the first day or two there is some limitation of respiratory motion on the painful side with perhaps a fine friction. There is no change in percussion note except perhaps a slight typanitic quality, but attention is directed to the probable area of affected lung by decrease or relative suppression of breath sounds. Here there are heard fine crepitant râles. Direct auscultation with the ear applied to the chest wall sometimes will allow the detection of distant bronchial breathing at the end of expiration before this is audible with the stethoscope.

By the second or third day the signs of *consolidation* are evident, but their appearance may be delayed yet longer in cases where the beginning lesion is centrally placed. Motion of the affected side is restricted and vocal fremitus is increased over the lung involved. A friction sound is heard over regions of pleurisy and sometimes a pleural fremitus is readily felt. The resonance on percussion is decreased and the note becomes dull. Vesicular breathing disappears and the breath sounds originating in the trachea and glottis are heard, *bronchial breathing* of an intense tubular character. Voice sounds are heard as if they originated within the chest.

and this *bronchophony* may have a high pitched nasal quality *egophony* Partial obstruction of the larger bronchi by exudate which interferes with the conduction of breath and voice sounds may be removed by coughing when obstruction is complete the voice and breath sounds are faint or absent *massive pneumonia*

Just above the consolidated lung the percussion note frequently has a higher pitched resonance (*Skoda's resonance*) With extensive involvement of a lower lobe the dulness may be so marked as to suggest the presence of fluid but usually the sense of resistance met with on percussion over fluid is absent

With the beginning of resolution crackling and bubbling râles are heard the breath and voice sounds become less bronchial and dulness decreases The final return to normal resonance and breath sounds usually is accomplished in a few days but the percussion note may remain high pitched for weeks

After a variable period of from five to ten days with continued dyspnœa rapid pulse and perhaps delirium and cyanosis a remarkable change occurs The temperature drops rapidly frequently with profuse perspiration the urgent dyspnœa and evidences of toxemia disappear and the patient passes from a condition of restless peril to one of relative comfort and quiet sleep *crisis* The rapid and welcome improvement which characterizes the crisis in pneumonia may occur within two or three hours but usually occupies a somewhat longer period When improvement is more gradual defervescence occurs more slowly *lysis*

In unfavorable cases the evidences of toxemia increase rather than abate cyanosis is deeper the face gray and drawn Extremities are cold and clammy the heart tones faint the pulse more rapid small and irregular Cough is ineffective and the accumulation of mucus gives rise to coarse rales and rhonchi which obscure the evidence of extension of the pneumonia to new parts of the lung In spite of such careful examination as can be made without unduly disturbing the patient necropsy may demonstrate involvement of the lung far greater than was indicated by physical signs The cause of death in pneumonia often is circulatory failure in some instances arising from overload of the right heart with dilatation in others from the direct effects of the toxemia and anoxemia with evidences of peripheral vasomotor paralysis Sometimes death comes apparently by respiratory failure with extensive lung involvement sometimes by reason of complications arising from local accumulation of pus or invasion of other organs by pneumococci or by the accentuation of the effects of preexisting cardiovascular or other disease Marked and persistent pneumococcemia is present in over half of the fatal cases

In a disease which presents so many symptoms and physical signs the variations and incidents of which will be referred to later it is to be anticipated that numerous departures from the classical picture will be encountered even in cases in which the combination of symptoms leaves no doubt as to the diagnosis The degree of toxemia which in turn is a function of several elements including the type and extent of pneumococcal infection and the physical condition and resistance of the patient varies greatly and often independently of the demonstrable extent of lung involvement Cases of all grades of severity are met with from those in which the infection is overwhelming from the outset to those in which pain and dyspnœa are minimal the pulse throughout of good quality and increased only proportionately to the moderate fever with recovery after a few days of slight or moderate illness These milder cases are frequent in private practice and contribute largely to the lower mortality in country and private practice as compared with the high death rates of metropolitan hospitals

Clinical Forms of Pneumonia

Peculiarities in the location and extent of the lesion of the lung give rise to special clinical forms of pneumonia Short attacks in which after a fairly typical onset the fever spontaneously falls within twenty four to forty-eight hours are known as *abortive pneumonia* In *central pneumonia* the lesion does not reach the periphery and frequently is so far distant from the chest wall that signs of consolidation are detected with difficulty on physical examination or only by x ray When the lesion is centrally placed and the toxemia relatively mild difficulty in diagnosis may arise as in the case of a nurse who became ill with chill fever and slight cough but continued with her duties until the third day when she was brought to the hospital There were no physical signs of consolidation no pain and no friction rub but a single specimen of rusty sputum and slightly increased respiratory rate suggested the diagnosis A radiograph showed a small area of consolidation in the right mid chest The temperature was normal on the fourth day and then distant bronchial breathing was heard in a small area over the right mid scapular region

Pneumonia at the apex of a lung often gives rise to unusually well marked signs of consolidation and is said to be associated with delirium more often than is pneumonia of equal severity elsewhere in the chest The pneumonic process in some cases involves several lobes successively *migratory pneumonia* In cases in which the exudate fills the larger bronchi breath sounds are not heard or are very faint over the consoli

dated dull area *massive pneumonia* and the presence of effusion is suggested

When by chance or by reason of reduced resistance pneumonia occurs in the course of other diseases such as nephritis valvular heart disease or diabetes it is likely to result in death and the condition then is sometimes called *terminal pneumonia* It is frequently difficult or impossible to determine whether a terminal pneumonia is lobar or bronchopneumonic in type Of such cases a number are the result of *aspiration* of regurgitated stomach contents

Pneumonia in the aged *senile pneumonia* is likely to be atypical the temperature relatively low and the prostration and general symptoms out of proportion to the slight and often obscure physical signs In alcoholics also the physical evidences of pneumonia may be slight and the clinical picture of delirium tremens overshadows the signs of infection In other alcoholic subjects however especially in vigorous laborers the symptoms of pneumonia may be outspoken and coincident with or shortly after the onset the delirium becomes acute with the usual hallucinations of delirium tremens

Secondary pneumonias occur in the course of other infectious disease and may be lobar or lobular in distribution The causative organism may be the pneumococcus or other of the bacteria commonly found in the respiratory tract Pneumonia frequently follows influenzal infection and while more often lobular is sometimes lobar and due to pneumococcal infection The kind of pneumonic infection which follows influenza seems to be determined by the organisms which happen to be present either in the respiratory tract of the patient at the time of the influenzal attack or widespread in the community

Anæsthetics and operations sometimes are followed by respiratory disease including lobar pneumonia The shock of operation chilling of the patient and irritation of the lung tissue by the anæsthetic may conceivably produce local tissue injury sufficient to allow pneumococci if present in the throat to obtain lodgement in the lung More often either localized atelectasis or bronchopneumonia results from the aspiration of mucus from the pharynx or of regurgitated stomach contents the organisms concerned being those present in the aspirated material Other instances of supposed lobar pneumonia are due to multiple pulmonary infarctions The term ether pneumonia is misleading since pneumonia occurs after chloroform anæsthesia and was noted following operations before anæsthetics were employed It occurs also after operations under local anæsthesia

Relapse occurring in a patient who has been fever free for a few days

is unusual and in those cases which have been studied adequately often is due to pneumococcus of a type other than that causing the original infection as in Stillman s case in which a type II infection followed two days after exposure to a type II case in a patient convalescent from type I pneumonia As noted by Cecil such clinical relapses are more likely to occur in pneumonia wards in which the chances of cross infection are offered although he encountered some type I relapses in type I patients Subsequent reinfections by streptococci were noted in U S Army hospitals in 1918 and often were fatal

Recurrence at intervals of months or years is met with more often in pneumonia than in the other infectious diseases with the exception of erysipelas In explanation of the many attacks over a period of years it has been argued that one attack predisposes to subsequent infections but perhaps a more rational explanation is offered by the assumption that the level of natural immunity is lower than the average in these susceptible persons and fails to protect under repeated minor exposures incident to community life While the successive attacks may be due to different types of pneumococci instances of repeated infections by a single type have been seen as in the cases of recurrent type III infections studied by Cecil He suggested the possibility of a chronic focus such as a sinus infection which might serve as a source of the reinvasions

SYMPTOMATOLOGY

Fever Chill and Crisis

The fever usually rises rapidly and a chill at the onset of pneumonia is so frequent as to be characteristic Chill at the onset occurred in two thirds of the Bellevue cases (Cecil) When the temperature rises more slowly the chill is less severe or absent In children vomiting and sometimes convulsions occur at the onset During the fastigium the fever curve is maintained with but little variation usually 103 to 104° F for several days and then may show greater fluctuations These greater variations occurring about the time of crisis are referred to as precritical fall or pseudocrisis and precritical rise and are of clinical interest in that they indicate a change in the course of the disease possibly crisis and recovery Such fluctuations in fever may be followed however by an accentuation of the illness and extension of the pneumonia to new parts of the lung A rapid rise of fever above the previous level in a seriously ill patient is ominous and often precedes death In persons weakened by other disease or advancing age the fever is likely to be lower and cases occur in which fever is slight or absent

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The day on which crisis will occur cannot be predicted An old tradition associated profuse herpes with crisis on the seventh day, and crisis has been believed to occur more frequently on uneven days Crisis may occur as early as the third day but statistics show that it occurs usually from the fifth to the ninth days most often on the seventh in keeping with the obvious probabilities In about one half of the cases of non fatal pneumonia usually including those in which fever is prolonged beyond the tenth day defervescence is by lysis Further persistence of irregular fever suggests some complication frequently empyema

The fall in temperature is but one expression of the turn toward recovery which marks the crisis With the decrease of fever there is profuse perspiration the symptoms of toxemia rapidly decrease the urgent dyspnea disappears without immediate change in the consolidation of the lung the pulse becomes slower and delirium is replaced by restful sleep The exact mechanism of recovery in pneumonia whereby in some patients the improvement is sudden and in others slower is not understood but probably is closely concerned with both antitoxic and bactericidal immunity Immune substances appear in the blood in measurable quantities about the time of crisis

The rapid subsidence of fever and the amelioration of other symptoms, which follow the administration of type specific pneumococcal serum, sufficient in amount to neutralize the circulating toxic products of the pneumococcus simulate closely the events of the natural crisis this parallelism suggests that the natural crisis may mark the period when the immune response of the body attains a magnitude sufficient to neutralize the toxic soluble specific substance of the pneumococcus in the blood

Cyanosis and Anoxemia

Studies on cyanosis and dyspnea have resulted in a clearer understanding of these frequent symptoms of pneumonia but there is still much to be learned concerning their exact mechanism Lundsgaard has shown that when the oxygen saturation of arterial blood is reduced to between 85 and 80 per cent cyanosis results from the increase of reduced hemoglobin in the blood further reduction in the oxygen saturation results in deeper cyanosis In cyanotic pneumonia patients there is a marked reduction in the oxygen saturation of arterial blood (Means Meakins Lundsgaard) and when oxygen is administered the cyanosis frequently clears with increase in the oxygen saturation of the blood It seems established therefore that to a large extent the cyanosis of pneumonia is due to anoxemia although other mechanisms may play minor rôles

Among the several explanations advanced to account for the anoxemia that of interference with oxygen intake in the affected lung may be considered first If we assume that a considerable area of one lung is involved and that it is no longer able to function in ventilation the blood passing through this portion will receive no new oxygen supply and mixing with the portion of blood passing through the normal lung may in time cause the entire mixture to attain an oxygen deficit sufficient to produce symptoms of anoxemia including cyanosis It has been estimated that about one third of the venou blood would have to traverse non aerated lung to produce this result While this mechanism is attractive in theory and indeed may account for some portion of the anoxemia in certain types of cases it fails to cover other known facts such as the almo t bloodless condition of the lung in gray hepatization the vascular obstruction in consolidated lung as demonstrated by gelatin injections the absence of arterial anoxemia in some cases of extensive consolidation and the clearing of cyanosis and relief of anoxemia under oxygen therapy in some cases of widespread lung involvement

Shallow and rapid breathing has been urged as the cause of anoxemia and cyanosis in pneumonia by Haldane Meakins and Priestly As breathing becomes more and more shallow the amount of air entering the lungs and bronchi grows progressively less until it may exceed by little the residual air in the bronchi (dead space approximately 150 c c) and the air in the alveoli is renewed in part or almost entirely by diffusion Normal oxygen tension in the alveoli is reduced and incomplete saturation of the blood results In support of this theory it was shown by Meakins and Davies that a normal arterial oxygen saturation of 94 3 per cent was reduced to 91 7 per cent by decreasing the normal tidal air of 500 c c to 315 c c and that further decrease in tidal air caused periodic respiration a symptom of anoxemia In patients with lobar pneumonia Meakins found cyano is when the volume of tidal air per respiration was reduced below approximately 240 c c In fatal cases the respiratory volume decreased still further and in the recovering cases the respiration volume increased the day after crisis and became approximately normal on the following day The observed simultaneous decrease in respi atory rate and of cyano is following the induction of pneumothorax in patients with pleurisy in lobar pneumonia is further evidence of the importance of rapid shallow breathing in the production of cyanosis

Alterations in the rate of diffusion in the alveoli also has been urged as a cause of cyano is Hoover suggested that a fine layer of fluid covering the alveolar walls would hinder the passage of oxygen and Brauer assumed an actual functional change in the alveolar epithelium and pro

posed the name pneumonosis for this hypothetical condition of the alveolar epithelium. In pulmonary edema following war gas poisoning, in some cases of influenza and in extensive bronchopneumonia the excessive moisture in the alveoli and frothy fluid in the bronchi undoubtedly interfere with the normal exchange of gases in the lung. These conditions are reproduced to some extent in cases of lobar pneumonia in which pulmonary edema supervenes or in those in which the disease is diffuse and extensive.

Dyspnea

The relation of rapid shallow breathing to anoxemia and cyanosis requires some further inquiry into the causes of hyperpnea and dyspnea in pneumonia. These causes comprise in part disturbances of the normal mechanisms of respiration and in part mechanical, nervous and metabolic factors associated with the pneumonia itself. Currently accepted theories as to the mechanism of normal respiration assume that the respiratory center is stimulated by increased CO_2 tension in the blood and by nervous stimuli reaching the respiratory center by way of the vagi. Voluntary increase in respiration with increased elimination of CO_2 is followed in normal persons by a period of apnea and an increase in the CO_2 of inspired air results in increased depth and rate of respiration. Porter and Newburgh found in dogs with pneumonia that exposure to increased CO_2 tension was followed by increased depth of respiration even after section of the vagi and that cocainization of the vagi was followed by a reduction of the respiratory rate from 60 to normal.

Increase in metabolism, which may amount to 30 per cent or more with the fever of pneumonia, results in an increase in CO_2 to be eliminated and to this extent favors increase in respiration. Pleural pain causes voluntary restriction of the depth of respiration as does also abdominal distention. To these effects is added the impairment of pulmonary function by the pulmonary involvement. Anoxemia tends to produce hyperpnea and in turn rapid shallow breathing contributes to anoxemia, thus completing a vicious circle in the pneumonia patient. It is thus evident that the dyspnea of pneumonia is dependent on a number of factors whose relative prominence may vary in different cases but which concern both the increased respiratory requirements arising from increased metabolism, anoxemia and possibly disturbance of acid base balance in the blood and decreased ability to meet these requirements through interference with normal respiratory mechanism. Stimulation of the respiratory center results first in increased activity but later in decreased sensitiveness

through fatigue and further impairment of the effectiveness of respiratory effort

The possible effects of anoxemia in contributing to some of the prominent symptoms of pneumonia are of clinical interest Restlessness insomnia psychic disturbances including delirium common in pneumonia are seen also in anoxemia due to oxygen lack in otherwise healthy persons such as those at high altitude and it is possible that these symptoms usually attributed to toxemia in pneumonia may be due in part to anoxemia Certainly they are more common in cyanotic patients Experimental anoxemia causes at first increased heart rate Heart block also has been noted The unfavorable effect of lack of oxygen undoubtedly contributes to the functional disturbance of the myocardium and the effects of anoxemia on heart muscle must be added to the recognized factors of increased temperature and metabolism obstruction to pulmonary circulation and toxemia which increase the load on the heart and tend toward cardiac impairment

Heart and Circulation

The toxemia anoxemia and increased metabolism of pneumonia as well as the increased mechanical strain arising from the obstructed pulmonary circulation impose an enormous burden on the heart and render the cardiac symptoms of first importance Many patients notably in the younger age group pass through pneumonia with no cardiac symptoms other than a moderate acceleration of the pulse Porter has shown that the heart muscle is not permanently injured in pneumonia In others especially those in the middle decades previously in apparent good health the stress of the disease makes evident preexisting damage to heart muscle and alarming and often fatal heart weakness appears in patients whose illness has seemed to be progressing favorably and at necropsy evidence of preexisting fibrous changes and old scars are noted

The pulse during the chill is small later it becomes fuller and bounding 100 to 120 per minute The pulse after crisis may be abnormally slow (bradycardia) The heart tones are clear the second pulmonic sound is accentuated and there may be a faint systolic murmur at the apex The blood pressure in favorable cases is not disturbed or may be lowered 10 to 20 mm Hg Increase of the right heart dulness with venous engorgement faint heart sounds with decrease in the second pulmonic sound shortening of the long pause and increase in the pulse rate are unfavorable symptoms Irregularity of the heart may have been present previously or may follow the use of digitalis but in a heart previously regular the

appearance of irregularity is often of serious import The relation of blood pressure and rapidity of heart beat to the prognosis in pneumonia is formulated in Gibson s rule when the arterial pressure expressed in millimeters of mercury does not fall below the pulse rate expressed in beats per minute the fact may be taken as an excellent augury while the converse is equally true Exceptions to this dictum at once present themselves particularly in cases of hypertension and in those with habitually low blood pressure A marked or sudden fall in blood pressure is ominous

Pain

Pain is present in about three fourths of the cases of pneumonia It is usually an early and often the first symptom noted It is felt most often in the nipple region or axilla of the affected side in pleurisy involving the central portion of the diaphragm pain may be referred to the shoulder or neck Not infrequently pain is referred to the abdomen suggesting appendicitis cholecystitis or some upper abdominal accident After the first few hours the pain may lessen but often it persists for days so that the patient dreads to move to cough or to attempt to speak He seeks a position in which the pain is least and often lies on or with the body curved toward the affected side

Respiratory Symptoms and Cough

The respiratory symptoms of pneumonia are a complex of the pain of pleural irritation with limitation of lung excursion of bronchial exudate and irritation of vagal fibers of toxemia dyspnea fever and later of the additional pulmonary embarrassment resulting from weakness of the right heart One or two of these factors may predominate or all may combine to produce the most distressing dyspnea and cyanosis Respirations are shallow 30 to 60 or more per minute and attempts of the patient to reduce the pain and distress of urgent breathing result in the expiratory grunt which though not peculiar to pneumonia is seen most frequently in this disease

Cough at the outset is dry painful and unproductive and comes in paroxysms later it may be less distressing with the expectoration of a variable amount of sputum

Laboratory Findings

Sputum — Rusty viscid sputum is perhaps the most characteristic single feature of lobar pneumonia It contains a large amount of fibrin

together with red cells leukocytes alveolar epithelium and pneumococci The expectoration is at first mucoid or blood streaked and later with the increase in degenerating red cells and fibrin acquires the reddish brown or rusty color and tenacious quality of typical pneumonic sputum The protein and chlorides are increased in the sputum of lobar pneumonia During resolution the sputum becomes lighter in color and less viscid, in some cases it is copious in amount in others scant Occasionally usually in severe infections the sputum is more fluid profuse and reddish brown resembling prune juice Rarely the first expectoration is profuse and bloody suggesting a pulmonary hemorrhage of tuberculosis In exceptional cases in adults there may be no expectoration or only a minimal amount of mucoid sputum In children the sputum usually is swallowed

Urine —The urine shows the changes seen in acute fever it is scant high colored and may contain traces of albumin The chlorides are decreased during the course of the illness and later during resolution the nitrogen content is increased In severely ill patients and in those in whom severe pain has required opiates retention of urine sometimes occurs The detection and relief of a distended bladder often contributes more than sedatives to the comfort of the restless patient

Blood —Leukocytosis of from 10 000 to 30 000 or higher is usual in lobar pneumonia Mild infections and overwhelmingly severe infections often are associated with low leukocyte counts Repeated counts from day to day usually show a progressive rise in polynuclear leukocytes in favorable cases in cases in which the leukocytes fail to increase or actually decrease the outlook is likely to be unfavorable although not invariably so Shortly after crisis the leukocytosis decreases A subsequent rise in leukocytes suggests some complication of these empyema is the most frequent

Blood Cultures —The significance of pneumococci in the circulating blood in pneumonia as an indication of the severity of the infection and consequently of the prognosis has occasioned much discussion Blood cultures in pneumonia have yielded positive results in 20 to 50 per cent of cases in the hands of most observers A few workers have obtained much higher percentages of positive cultures and have been inclined to regard pneumococcal bacteremia as of relatively minor importance in prognosis It is probable that in most infections whether mild or severe occasional organisms pass into the blood stream and oft repeated examinations of the blood increase the probability of their detection but in lobar pneumonia combined bacteriological and clinical experience indicate that pneumococcemia is associated usually with severe infection

The incidence and degree of bacteremia are important in estimating

the dosage of serum and in prognosis Bacteremia varies in frequency among the several types and its effects are reflected in their respective case fatality rates Of 1 719 cases of all types of pneumococcal pneumonia positive blood cultures were obtained in 24 8 per cent Of these positive cultures were found in 27 4 per cent of type I 38 7 per cent of type II and 29 7 per cent of type III Of 875 cases of types IV to XXXII positive cultures were obtained in 17 1 per cent (Bullowa and Wilcox) The percentages of positive cultures are higher in patients in age groups over 50 than in younger groups Complications such is empyema or pericarditis are more frequent in patients in whom bacteremia occurs and case fatality rates in serum treated as well as in untreated cases rise with the incidence and increasing degree of bacteremia

Skin

Herpes involving the lips and nose is frequent in pneumonia and often is of diagnostic value The face is flushed sometimes more on the affected side Cyanosis is present in the more severe cases In children a transient red rash at onset with vomiting and fever may lead to the suspicion of scarlet fever but the quick subsidence and lack of punctate appearance of the rash distinguish it from that of scarlet fever During the fastigium of the fever the skin is hot and often dry although sweating which usually is profuse at time of crisis may be noted throughout the illness Cold clammy and cyanotic extremities and face often mark the later hours of cases with fatal termination

Abdominal Symptoms

Abdominal pain at the onset of pneumonia often leads to a mistaken diagnosis of appendicitis cholecystitis or acute pancreatitis with in some cases resulting operation In exceptional instances early nausea vomiting and diarrhea with fever and severe toxemia and relatively few respiratory symptoms distract attention from the lung in which signs of consolidation appear later in the disease During the course of the more severe pneumonias meteorism is frequent and occasionally there is acute dilatation of the stomach More rarely colitis with pseudomembranous inflammation of the bowel occurs Pneumococcal peritonitis is a relatively rare complication Jaundice is not uncommon The liver may be depressed by a right sided pneumonia or may be enlarged in association with cholangitis or with passive congestion The spleen usually is slightly enlarged as the result of acute infection and occasionally is palpable

Nervous Symptoms

The nervous symptoms of pneumonia are referable largely to the toxemia and possibly also to anoxemia Headache is frequent at the onset and in children convulsions may initiate the illness There may be delirium varying from mild incoherence in some cases to wild excitement and violence in others Maniacal delirium may come on suddenly so that the patient with pneumonia requires constant attention The necessity of suitable protection of windows in home and hospital is emphasized Aged and otherwise weak patients are more likely to be stuporous often with muttering delirium and relatively quiet In alcoholics delirium may occur as in other patients with pneumonia or the infection may precipitate delirium tremens in a patient already prepared by alcoholic excess Symptoms of meningeal irritation without evidence of actual meningeal infection meningismus sometimes appear and then subside Postinfectious psychoses occasionally follow severe infections including pneumonia but in general offer a good prognosis More rarely seen after pneumonia are peripheral neuritis and the more serious conditions of hemiplegia encephalitis and myelitis

COMPLICATIONS

Empyema is a frequent complication of lobar pneumonia In case in which pain is severe and prolonged indicating extensive pleural involvement empyema is more likely to follow than in cases with less degree of pain The purulent exudate may occupy the entire pleural cavity on the affected side or may be restricted in extent by adhesions to a portion of the cavity adjacent to the chest wall or may be found only between lobes of the lung

Pulmonary abscess and *pulmonary gangrene* are relatively rare complications which result from failure of the normal processes of resolution When the physical signs in the chest fail to return to normal as quickly as usual following pneumonia the condition sometimes is referred to as *delayed resolution* or *unresolved pneumonia* Instead of the physical signs clearing up rapidly they persist there may be dulness with or without bronchial breathing and with or without rales lasting for several weeks Very often there is no fever but convalescence is less prompt than usual In a few cases the temperature fluctuates above normal In time physical signs return to normal and recovery is complete While instances of delay in resolution without other complications occasionally occur the ready acceptance of this diagnosis especially where there is a slight daily fever

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Complications

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frequently leads to the overlooking of conditions such is empyemi and lung abscess Errors are far less frequent when physical examination is supplemented by x ray examination Very rarely there is actually an unresolved pneumonia a lung in which organization of the exudate is taking place Such cases if not fatal result eventually in fibrosis of the affected part of the lung possibly with bronchiectasis

Pericarditis fibrinous or seropurulent is not infrequent in the more severe pneumonias Acute *endocarditis* sometimes follows pneumococcal pneumonia and becomes clinically evident shortly after apparent recovery from the pneumonia

Pneumococcal *meningitis* may occur at the onset of the infection and cause death before the physical signs of pneumonia are clearly marked or the meninges may be infected during the course of pneumococcic bacteremia or later in association with acute endocarditis Treatment by serum and sulfapyridine has resulted in cures of this formerly almost always fatal complication

Other rarer complications result from the localization of pneumococci from the blood in various parts of the body such as muscle bone glands or joints with the production of abscesses or arthritis Thrombosis of the femoral and other veins is noted sometimes Otitis media and mastoiditis may occur during the course of pneumonia or as a sequel in adults, in children they are much more frequent especially in infections by the types with higher numbers

The succession of complications which may occur in pneumonia is illustrated by the case of a man in whom after a stormy onset with fever and severe pain referred both to the upper abdomen and right lumbar region the signs of consolidation appeared over the right lower lobe and then four days later over the left upper Hiccough and meteorism were troublesome Ten days after the onset the fever was much lower and he seemed better but when seen again with his physician four days later a right interlobar empyema was found After surgical drainage of the chest he improved but the fever began again to increase Careful adjustment of drainage tubes failed to result in decrease in the fever and physical examination and x ray films indicated complete drainage of the empyema The heart which up to this time had seemed normal aside from a faint systolic murmur present from the onset of the illness became more rapid and irritable and the murmur louder A few conjunctival and cutaneous petechiæ appeared and the pneumococcus was recovered in culture from the blood He died six weeks after the onset of pneumonia At necropsy healing empyema and acute pneumococcal mitral and mural endocarditis were found

Diagnosis

The curative value of type specific antipneumococcal serum and of sulfonamides has laid increased emphasis on the desirability of early bacteriological diagnosis both of lobar pneumonia and of bronchopneumonia of respiratory origin also frequently caused by the pneumococcus Physical diagnosis based on observation by eyes hands and ears remains however of basic importance and constitutes the first line of attack on the illness of the patient

The great forward strides in serum and drug treatment of pneumonia have tended toward more emphasis on the bacteriology of the disease and it has been well said that the diagnosis is now bacteriological rather than anatomical It may not be out of place however to note that clinical symptoms and signs still are valid and are available to the physician even before he can receive advice from the laboratory Physical diagnosis in pneumonia still is important

Lobar pneumonia presents so many symptoms and signs among which are likely to be chill fever pain rapid respiration herpes rusty sputum leukocytosis crepitant râles dulness on percussion and bronchial breathing that the diagnosis in a typical case offers no difficulty especially if the patient is seen repeatedly Nevertheless difficult problems of diagnosis arise in cases in which some one symptom such as pain or toxemia is unusually prominent at the onset or when the patient is seen late in his illness or in cases in which age and weakened physical state contribute to make the clinical picture atypical A careful history here is as always of great assistance With sudden onset of fever severe headache vomiting and toxemia without pain or cough it may be impossible during the first hours to tell whether the patient has pneumonia or one of the other acute infectious diseases such as meningitis or scarlet fever At succeeding visits other symptoms or signs of pneumonia such as increased respiratory rate cough pain crepitant rales or absence of signs of other diseases usually will make the diagnosis clear

Pain while usually felt in the nipple region side shoulder or upper chest may be referred to the abdomen and the clinical picture may resemble that of appendicitis cholecystitis acute pancreatitis or other abdominal accident associated with sudden pain In cases in which the other symptoms or signs of pneumonia are slight or absent and in which also the clinical signs of the simulated disease are known to be misleading or uncertain such as appendicitis in children the apparent urgency for surgical interference has led frequently to unnecessary operations

Pneumonia in the aged and in those weakened by other diseases often presents an insidious onset and atypical course with relatively slight or even no fever and only moderate increase in the respiratory rate In such patients with an unexplained illness pneumonia always should be considered a possibility

The absence of the usual physical signs of crepitant râles and consolidation for several days (*central pneumonia*) or delay in their appearance should not interfere with the diagnosis where other symptoms and signs of pneumonia are present, but in cases atypical in other respects, the diagnosis may remain long in doubt Careful auscultation high in the axilla sometimes will yield the earliest physical signs of the pneumonic process The importance of auscultation with the ear to the chest has been referred to already in the early recognition of bronchial breathing

The laboratory often affords valuable confirmatory and, in some instances determinative evidence Pronounced leukocytosis is the rule, but in severe cases sometimes there is leukopenia Blood cultures may show the pneumococcus, especially in severe infections The sputum often is characteristically rusty and tenacious but may be mucoid or blood streaked Microscopic examination will show the organisms present as well as the cellular content and increase in fibrin The pneumococcus is isolated by appropriate methods and further information gained as to the type concerned in the disease Examination of the urine for decrease in the chlorides has been employed in diagnosis but, in comparison with the other data usually available seems of minor value

The x ray by the use of the portable machine can be employed without unduly disturbing the patient and is extremely helpful in the detection of deeply placed lesions in the interpretation of confusing physical signs and in observing the progress from day to day of the lesion in the lung But the ready availability of the x ray should not constitute an excuse for its abuse, either through the development of careless habits in physical examination or through the disturbance of the patient by repeated moving to the laboratory

When the patient with an atypical history is first seen late in the illness, there may be difficulty in determining whether the physical signs in the chest are due to consolidation or effusion or to both This situation is also met with in severely ill patients under continuous observation by reason of the slow accumulation of pus in the pleura during and after the height of the pneumonia In other infections such as tuberculosis and the streptococcal bronchopneumonias following measles influenza and upper respiratory infections common during the World War I pleural effusion is frequent and where the history is not clear or symptoms indefinite the consolidation of lobar pneumonia has to be considered Large effusions occurring early in the illness are likely to be due to infections other than that of lobar pneumonia Pronounced and persistent dulness of flatness on percussion with absent breath sounds and decreased or absent tactile fremitus and displacement of the heart suggest effusion Where consolidated lung lies beneath fluid bronchial breathing may be heard and the voice sounds be well transmitted Egophony just above the area of flatness is a valuable though not absolute, sign of fluid Flatness on one side of the chest from base to clavicle and the bulging of

the interspaces strongly suggest fluid Dyspnea frequent in rapidly developing effusions may be absent in the presence of large empyemas where the pus accumulates slowly Small collections of pus and those situated in the interlobar spaces give rise to relatively slight physical signs and often are missed unless the chest is examined carefully The x ray here is of great assistance

In all cases of *suspected fluid* the exploring needle should be used A careful consideration of all the physical signs followed by exploratory puncture repeated if necessary with due regard to the anatomical position of the liver heart and vessels intercostal arteries and lobar boundaries will solve most of this group of problems Fluid or pus if found in large quantity should escape slowly and not over one to one and one half liters should be removed at one sitting Acute pulmonary edema and albuminous expectoration which may follow the rapid evacuation of large amounts of fluid present a picture which though rare is better avoided than seen Pneumococcal empyema when small sometimes is absorbed following removal of part of the pus by the exploring needle but surgical drainage usually is necessary unless penicillin is used Pneumococcal pus is likely to be thick or creamy yellowish or greenish yellow in contrast to the pus of streptococcal empyema which is often a thin cloudy fluid Microscopical and cultural examinations should be made

Pericarditis is as already noted frequently overlooked largely because it occurs in the more seriously ill patients either as a late event or at a time when the friction if audible by reason of the position of the portion of the pericardium involved is likely to be obscured by other sounds of pulmonary origin Pericardial friction also has to be distinguished from friction sounds originating in the pleura adjacent to the heart which have a combined respiratory and cardiac rhythm In cases exceptionally favorable for diagnosis pericardial effusion may be recognized in lobar pneumonia

Bronchopneumonia occurs as a primary disease in small children and in the aged In adults it is as a rule secondary to some other disease In primary bronchopneumonia of adults the pneumococcus has been found in something over 50 per cent It would seem misleading however to apply this percentage to figures dealing with the gross incidence of diagnosed bronchopneumonia in adults The wide distribution of subcrepitant rales usually over both sides of the chest and in the lower lobes the absence of symptoms of onset characteristic of lobar pneumonia in the adult and preceding illness such as measles whooping cough bronchitis or influenza aid in distinguishing bronchopneumonia from the lobar form It is a frequent terminal event in chronic diseases such as nephritis heart disease and in conditions in which lowered sensitiveness of the larynx and upper bronchi allows the aspiration of mucus blood food or other foreign particles While the multiple pneumonic foci may coalesce to produce continuous areas the physical signs of consolidation are less clearly defined than in lobar pneumonia

The difficulty of distinguishing between lobar and bronchopneumonia is especially great in children and as Griffith has shown, even when clinical observation is reinforced by the x ray the necropsy may fail to confirm the antemortem diagnosis This uncertainty in diagnosis is reflected in the opinions of pediatricians as to the relative frequency of bronchopneumonia and lobar pneumonia in children up to two years of age the figures varying from a ratio of 16 to 1 to a ration of 0 51 to 1 In another tabulation of reports which included infants and children up to 10 years the ratios varied from 6 to 1 to 0 31 to 1 These figures were no doubt obtained under varying epidemic and other conditions but as Griffith points out they represent the statistics on which relative frequency must be based

TABLE II

PRIMARY ATYPICAL PNEUMONIA (*Cole*)

Bacterial Incitant	Number of Cases	Recovered	Died	Per Cent Mortality
Pneumococcu	39	36	3	7 [illegible]
Streptococcus	83	47	36	43 3
Staphylococcus	19	6	13	68 4
Influenza bacillus	8	7	1	12 5
Friedländer s bacillus	7	2	5	71 4
Bacillus mallei?	1	0	1	100
Mixed infection	26	18	8	30 7
Unknown	28	27	1	3 5
Totals	211	143	68	32 2

While the majority of acute pulmonary infections fall fairly readily into the usual clinical classification of lobar pneumonia bronchopneumonia and acute bronchitis there are encountered now and then adult cases which differ on the one hand from pneumococcal lobar pneumonia in their onset and course and in which the distribution of lesions in the lung is diffuse rather than lobar and which on the other hand seem to be primary in that they do not follow in the wake of other diseases as is usually expected in the bronchopneumonias of adults Bacteriological studies show a varied etiology In some the pneumococcus has been obtained, in others streptococci staphylococci and other organisms Cole in his discussion of acute pulmonary infections (De Lamar Lectures 1927–1928) emphasized the importance of primary atypical * pneumonia in adults (see Table II)

Streptococcal pneumonia was prevalent in 1916 In the widespread streptococcal infections of 1917–1918 many cases of penumonia and empyema followed

* Atypical is not used here in the sense now generally understood i e nonbacterial or virus pneumonia

measles but there were also numerous instances in which so far as could be learned the pneumonia was not preceded by other diseases Cases of acute pulmonary infection associated with a green producing streptococcus similar to that described by Mathers are met with sometimes In some of these the pulmonary lesion is diffuse as shown by physical and x ray examination in others a considerable portion of one lobe is involved Staphylococcal pneumonia was described by Chickering following influenza and has been noted also by Cole as a primary infection The profuse pinkish or reddish purulent sputum is suggestive of this form A few instances of primary pneumonia due to Friedlander s bacillus and to the Pfeiffer bacillus are noted in Cole s series

Of interest in the diagnosis of pneumonia as it is met clinically are those rare cases in which microorganisms generally concerned with other types of disease invade the lung Two instances will suffice to illustrate In the course of a local epidemic of meningitis a man was brought in following a chill with the symptoms of severe acute infection and signs of consolidation of the right lower lobe At necropsy the lesion in the lung was of lobar distribution and cultures showed the meningococcus in pure culture A man in the fourth week of demonstrated typhoid fever had a chill recurrence of continued fever without abdominal symptom and with the appearance of signs of consolidation in the lung The mucoid sputum contained typhoid bacilli on repeated examination but no pneumococci

As inflammatory diseases of the lungs have been more completely studied it has become evident that there are groups of cases in which no bacterial agent can be found Such cases are often clearly epidemic in incidence usually of low case fatality and often associated with diseases of now known virus origin Others are associated with rickettsial and toxoplasmal infections They have been grouped under the general heading of nonbacterial pneumonias In this group there may be included the syndrome described by Loeffler and others in which a migratory type of consolidation with fever and pronounced eosinophilia has been noted The early cases were found in persons returning from the tropics in whom various parasitic infestations were present also but other cases have now been found without tropical exposure and without demonstrable evidence of parasite infestation They are not tuberculous although the question of tuberculosis often is raised An allergic as well as a possible viral origin have been suggested

Other diseases and conditions simulate lobar pneumonia and require consideration in differential diagnosis *Acute tuberculous pneumonia* may begin with a chill subsequent cough fever and signs of consolidation The continuation of the fever with perhaps a more remittent course beyond the period usual in pneumonia should lead to further investigation including examination of the sputum for tubercle bacilli In tuberculous pneumonia the breath sounds often are less well heard even when other signs of consolidation are present and there may be

evidence of tuberculosis elsewhere in the lung or pleura A history of previous tuberculosis or hemoptysis is suggestive The x ray film may show evidence of an old apical lesion or of tuberculosis on the opposite side In tuberculous pneumonia of more gradual onset and course there is less likelihood of confusion with lobar pneumonia It is of course possible for lobar pneumonia to occur in a patient who also has pulmonary tuberculosis

The pulmonary lesions of *blastomycosis sporotrichosis* and *actinomycosis* are likely to have a chronic course and therefore, rarely will be confused with lobar pneumonia

Pulmonary embolism in which the onset is sudden with pain in the chest, cough dyspnea and expectoration of blood or bloody mucus, may resemble a beginning lobar pneumonia When the emboli are numerous, the infarcted areas may coalesce with resulting physical signs of consolidation Pulmonary embolism following operations particularly those on the abdomen and the prostate often is diagnosed erroneously as post operative pneumonia The involvement of the lower lobes in subjects of chronic heart disease with failing compensation or following operations and the expectoration of blood with low fever and absence of the signs of general infection point to pulmonary infarction

In children as well as in adults septic infarcts originating from a local infection such as otitis media with or without associated empyema, may give physical signs which combined with the general symptoms of an acute infection, lead to a diagnosis of lobar pneumonia

Hypostatic and aspiration pneumonia and atelectasis occur in person with weakened circulation or with abdominal distention and following operations and fractures in which the patient lies continuously on his back

Massive collapse of one or more lobes of the lung usually the lower may simulate pneumonia The onset is sudden with dyspnea and perhaps mucoid expectoration There is retraction of the affected side with relative dulness tubular breathing and absence of rales The heart and mediastinum are drawn to the affected side The condition has been ascribed variously to long maintenance of one position during operations to partial paralysis of the diaphragm and to the obstruction of a bronchus by mucus or other material Instances of quick recovery have been noted under the fluoroscope on change of position

Prognosis

The employment of antipneumococcal serum later the sulfonamides and more recently penicillin has greatly reduced the case fatality of lobar pneumonia in the several categories of cases arranged for example by type by age groups or by severity of onset and course as expressed by bacteremia The possibility that other effective antibiotics with high antibacterial power and low toxicity may be

developed in the future must be borne in mind One of the advantages of penicillin over sulfonamides is that the action of penicillin is not inhibited by the presence of pus tissue autolysates blood or serum Already some twenty or more substances which limit the growth of bacteria have been found but most of these possess also toxic qualities which prevent their use in the animal body

The most extensive figures gave a general mortality in the days prior to serum and chemo-therapy of slightly over 20 per cent (Wells 20 4 per cent Musser 1 6 per cent in 43 455 cases) Hospital mortalities are somewhat higher Osler in six years at Baltimore had a mortality of 30 4 per cent in 658 cases excluding 25 cases of terminal pneumonia, the mortality was 26 4 per cent In 6 531 cases in Cook County Hospital Chicago in seven years 1917-19 4 F B Kelly found a case fatality of 36 per cent Case fatalities varied in the individual years between 34 and 41 4 per cent with the exception of 1921 when only 26 6 per cent died In that year both the incidence and case fatality of pneumonia were low In Chicago there were but 1 007 deaths in 1921 whereas in 19 0 there were 1 3 and in 19 2 1 508 In the entire registration area of the United States there were 37 871 deaths from lobar pneumonia in 1921 while in 1920 there were 64 001 and in 1922 47 031 In Cook County Hospital in 1901 the case fatality was 36 per cent in 338 cases (Ingals) and in 1910-1920 37 1 per cent in 3 439 case (Tice and Herndon) In Bellevue Hospital the death rate has varied considerably from year to year ranging from 30 per cent to almost 50 per cent (Cecil) In the Massachusetts General Hospital over a period of 95 years Shattuck and Lawrence found variations of annual case fatality from 16 per cent to 40 per cent but when the cases were grouped by decades the case fatalities for 10-year periods were between 25 per cent and 31 per cent All of these statistics as to mortality antedate treatment with serum or chemotherapeutic agents

Hospitals especially those in large centers of population are likely to receive patients who have not done well at home and those whose living conditions contribute to lowered resistance to disease so that the case fatality rates of hospitals are much higher than the case fatality in private practice

The age of the patient is important In children over five years and in young adults the mortality is lower than in middle age in the aged the mortality is very high Kelly found the case fatality in Cook County Hospital for the several age groups to be essentially a curve beginning moderately high in the first 10 years of life at 20 3 per cent going down to 13 5 per cent in the second decennium then rising approximately 10 per cent with each decennium Cecil estimates the hospital fatality increase as 10 per cent with each decennium While comprehensive statistics of case fatalities by decades are not available for all ages it seems reasonable to assume that they will follow a curve similar to that of the hospital group but of lower altitude in the earlier decades

In U S Army camps from September 1917 to March 1, 1918 there were

953 cases of lobar pneumonia in which bacteriological determinations showed that the pneumococcus was present alone the mortality was 9.9 per cent. The men in these camps were almost entirely within the draft age 20 to 30 years so that the mortality may be taken as fairly representative of the decennium 20 to 30 under average conditions in a group from which most of the physically defective had been excluded.

The death rate from lobar pneumonia has varied in different epidemic periods. Besides probable variation in general virulence relative to host resistance it is possible that variation in prevalence of the several types of pneumococci, whose virulence is known to be different, influences the mortality rate in special communities. Case fatality rates vary with the several types. Collected cases for the United States and Canada give a case fatality rate for type I of 28.1 per cent, for type II 37.1 per cent, for type III 45.4 per cent, for type V 3[illegible].6 per cent, type VII 24.5 per cent, for type VIII 22.9 per cent (Heffron). The case fatalities of the higher numerical types average somewhat lower.

In addition to these general considerations the prognosis in the individual patient is influenced by his physical condition, the extent of the pulmonary lesion and the severity of the toxemia. Pronounced bacteremia, as shown by blood cultures and the absence of leukocytosis are of serious import. Previous diseases such as diabetes or nephritis, serious impairment of the heart resulting from valvular disease or from hypertension and weakened organs and tissues following exposure or excessive use of alcohol make the outlook more grave. The necropsy in persons dead of pneumonia frequently reveals preexisting disease of vital organs, of which there had been no recognized symptoms prior to the fatal illness. During the course of the illness the occurrence of complications such as pericarditis, endocarditis or empyema adds greatly to the risk.

While we thus have some indications as to the probable outcome of lobar pneumonia in a group of persons of given age and similar type and severity of disease we still are at a loss to predict the result of pneumonia in the individual case. Even in the favorable age group 20 to 30 years statistics show that without specific treatment about 10 per cent die, and there is no way of foretelling to a certainty that a given individual will be one of the 90 per cent who will recover. Careful weighing of factors such as relative severity of onset in the patient, the observed virulence of pneumonia in other patients in the local epidemic, the presence of demonstrable bacteremia, the degree of prostration and extent of lung involved, as well as the presence of known physical defects in the patient will assist greatly in a tentative estimate of his chance of recovery. In the higher age groups the possibility of unexpected and unfavorable outcome is multiplied. Patients seemingly progressing favorably suffer from an extension of the disease in the lung or develop alarming heart weakness and on the other hand those profoundly ill whose lives are despaired of for days recover.

Treatment

The revolution in the treatment of lobar pneumonia with the marvelous reduction in case fatality constitutes one of the most dramatic chapters of medicine. The early attempts at specific therapy began with the antipneumococcus serum of Fraenkel which failed in practical application to a large extent by reason of lack of knowledge of the existence of multiple types of pneumococci. Then came type I serum to be followed by specific sera for a number of other types. The recognition of multiplicity of types, now over 60 in number, as determined by the specific qualities of the capsular substance also explained many of the puzzling features of epidemiology and contagion and of the toxic symptoms of the disease itself. Hardly had serum begun to be widely applied when the sulfonamides appeared and successive derivatives have increased the armamentarium of the physician. The more recent discovery and availability of penicillin and allied substances have added still more to the means of combatting lobar pneumonia as well as other serious infectious diseases and the case fatality has been reduced to an amazing extent. With an understanding of some of the mechanisms of infection and recovery from lobar pneumonia has come recognition of the importance of the application of therapeutic agents at the earliest possible time in the illness. Knowledge of the rôle of anoxemia and improvement in methods of using oxygen have added much to the value of this adjunct in treatment. While not all patients can be cured, in general it may be said that case fatality rates can be reduced now to perhaps a tenth of those in the untreated disease in persons otherwise healthy. There still remain, however, the fatal residues of those in whom lobar pneumonia is the terminal event in bodies already undermined by chronic but unrelated disease as well as in those in whom treatment is delayed by various circumstances beyond the time when recovery is possible. In rejoicing in this gratifying therapeutic achievement it is to be remembered that all this did not happen by accident but is the summation of years of patient study and work by many men in many sections of research both in ancillary fields of chemistry and physics and in the more closely related fields of medicine.

General and Symptomatic Treatment

When the patient is first seen the question arises as to whether he should be treated at home or taken to a hospital. Many circumstances will influence the decision in each case. In general the requirements of adequate treatment are better met in a well equipped hospital than at home. Transportation in the early hours of pneumonia usually can be accomplished without harm with modern ambulance equipment.

In the case of the pneumonia patient every effort should be made to spare him

all unnecessary disturbance including that of visitors This conservation of his energy becomes doubly important with the added manipulations necessitated by serum or drug treatment The sick room should be well ventilated, cool but not cold Physical examinations by the physician should be accomplished with a minimum of movement of the patient Forethought in arrangement of feedings and the giving of treatments and in examinations will save the patient much unnecessary movement

In a disease of short course the maintenance of general nutrition is not a serious problem The diet should be easily assimilable and should supply an average of 2 500 calories Each patient presents a separate problem in which his likes and dislikes should be considered as well as any special questions such as impending alkalosis or abdominal distention Milk purees cereals, fruit juices, and when the patient is able to take solids bland foods suited to his desires are allowed Some patients are unable to take milk in others the sugar content of the diet must be reduced Alkalosis is at times met with in pneumonia and may require reduction in citrus fruit juices Estimations of blood chlorides and carbon dioxide combining power will be helpful guides in cases in which alkalosis is suspected

Sufficient fluid intake should be assured so that a urinary output of 1 500 to 2 000 c c is maintained Large amounts of fluid are lost by profuse perspiration and a daily fluid intake of 3 000 to 4 000 c c or more is required When sufficient fluids cannot be taken by mouth subcutaneous or intravenous transfusions of 5 per cent glucose may be given In regulating fluid intake some regard must be had to the therapy employed When sulfonamides are given sufficient fluid intake and urinary excretion are necessary to avoid precipitation of crystals of the drug in the tubules of the kidney In the use of penicillin on the other hand excretion of which occurs rapidly by the kidney some reduction in urinary output is desirable in order that an effective blood level of penicillin may be maintained Intravenous medication should be given with due regard to the condition of the heart and pulmonary circulation Blood transfusions may be helpful sometimes where anemia is marked

A laxative preferably a saline sufficient to give a free movement of the bowels should be given at the beginning of the illness and if necessary repeated to maintain a daily movement without severe purgation A daily enema may be substituted provided it does not occasion distress to the patient Hydrotherapy in the form of cool sponges given with a minimal disturbance improves vascular tone and often adds to the comfort of the patient

The use of drugs other than those having a specific effect on the pneumococcal infection should be confined to those required to meet such special situations as arise in the individual patient The pain of pleurisy often is relieved by the ice coil or ice bag Strapping or the use of a swathe about the chest may be resorted

to as a temporary measure in some cases Acetylsalicylic acid and bromides in usual doses or codeine 15 to 30 mgm (gr ¼–½) often will be sufficient to relieve pain and restlessness For extreme pain unrelieved by other measures morphine 7 5 to 10 mgm (gr ⅛–⅙) may be given in the first two or three days of pneumonia Later morphine should be used with caution because of its depressant action on the respiratory center and of the possibility that it may contribute to abdominal distension Sleeplessness often troublesome may be controlled with chloral hydrate bromides or morphine In patients with preexisting heart disease or in those in whom evidences of heart weakness appear digitalis in effective dosage is given The official U S P tincture (dose 1 c c or 15 minims) or the powdered leaf (0 065 to 0 1 gm gr 1–1½) will meet the requirements for oral administration Several preparations suitable for hypodermic or intramuscular use including U S P injectio digitalis (average dose 1 c c = 1 U S P unit) are available for those cases in which by reason of gastric disturbance or the necessity of rapid action the drug cannot be given by mouth

Dilatation of the right heart with evidence of venous stasis may be relieved sometimes by venesection with the removal of 100 c c to 200 c c of blood The occasions for such treatment are less frequent with the introduction of specific therapy

Vasomotor paralysis characterized by low blood pressure rapid small pulse and profuse sweating frequently mark a threatened fatal outcome Epinephrine solution ½ to 1 c c (minims 10–15) every 20 minutes until the blood pressure improves or caffeine with sodium benzoate 0 6 to 1 gm (gr 10–15) may be given hypodermically Coramine 1 5–3 0 c c (minims 2 to 45) may be used Strychnine and camphor formerly widely used are now less highly recommended Atropine is of value in the presence of excessive secretion and in pulmonary edema

Oxygen Therapy

The need for an additional supply of oxygen varies greatly in pneumonia as does opinion as to frequency with which oxygen therapy should be used Some hold that it should be employed in all cases others would use it only in those cases in which oxygen lack is evidenced by cyanosis The causes of cyanosis already discussed seem to be several including shallow rapid breathing in which the available air reaching the alveoli is greatly reduced and the interference with oxygenation by extensive consolidation of lung tissue The results of anoxemia in addition to cyanosis of varying grade are restlessness sleeplessness and delirium Rapid respiration which contributes to the development of anoxemia may also result from it as a compensatory measure There is evidence that anoxemia is detrimental to heart muscle kidneys liver and other organs When

the oxygen concentration in inspired air is sufficiently increased the respirations are slowed, and the patient becomes more quiet and often falls asleep

Except when an oxygen room is available in a hospital, the oxygen tent is the most effective method of administering oxygen a number of types are available, of which the motor driven tents are preferred by many The oxygen concentration in the tent can be maintained at from 45 per cent to 70 per cent by a flow of from 6 to 10 liters of oxygen per minute The use of the tent requires continuous nursing supervision care to avoid leakage and repeated testing to ascertain that the calculated amount of oxygen is actually being supplied

When the tent is not available and in some instances in which patients object to the tent oxygen may be given by nasal catheter A No 12–14 soft rubber catheter is inserted into the nose so that the tip reaches a point in the pharynx about the level of the uvula and is held in place by adhesive tape to the nose and forehead Oxygen so used must be humidified by passage through a series of two water bottles The flow of oxygen to maintain an oxygen concentration of 40 to 60 per cent is from 8 to 12 liters per minute

The catheter is cleaned and changed to the opposite nostril every six hours Other methods of administration include modifications of face masks some of which are effective and less irritating than the catheter In administering oxygen it is important to attain a sufficient concentration to relieve cyanosis and lower respiratory rate

Immune Serum Therapy

The introduction of effective sulfonamides and latterly of penicillin in the treatment of lobar pneumonia has relegated treatment by immune serum from a major to a minor place in therapy However there still may be cases in which a combination of serum treatment with one or the other more easily applied measures may be of help in desperate cases Consequently it has seemed desirable to continue a discussion of the methods for its use

Immune serum now is derived by immunization of the horse or the rabbit with cultures of one or another type of pneumococcus It contains the same kind of antibodies opsonins agglutinins precipitins and protective substances as those demonstrable in the blood of patients recovering from pneumonia Among the evidences of the specific action of the serum are the promotion of phagocytosis with the destruction of pneumococci and the neutralization of the soluble specific carbohydrate produced by the pneumococcus At the beginning of the disease conditions in the lung are much more favorable for the serum to accomplish these results than later when circulation of the blood is more impaired by the alveolar exudate in addition the total lethal products of the pneumococcus in the blood require less neutralizing serum The importance of early treatment is thus again emphasized

While successful serum therapy was first carried out with antipneumococcic horse serum that derived from the rabbit has largely replaced it A highly concentrated serum is made more easily The physical size of the rabbit serum molecule is smaller than that of the horse allowing better penetration and diffusion in the body and fewer individuals are sensitive to rabbit than to horse proteins In type III infections also rabbit serum has been more effective than horse serum

THE TYPING OF PNEUMOCOCCI —At the onset of pneumonia the clinical symptoms including the sudden explosive character of the onset and the appearance of other suggestive signs and symptoms often will indicate at once that the illness is lobar pneumonia and presumably (in 95 per cent of cases) due to the pneumococcus In other less typical cases the nature of the illness in the early hours is not so clear In still other cases the disease may turn out later to be a bronchopneumonia which however in a considerable proportion of cases associated with upper respiratory infections is due to pneumococcal infection In order that the proper type specific serum may be given in cases of pneumococcal origin and also that suitable chemotherapy may be applied in pneumococcal or streptococcal infections the bacteriological diagnosis including determination of pneumococcal type is of primary importance With increasing use of sulfonamides and penicillin the need for typing has greatly decreased in some excellent clinics no longer is it carried out except in exceptional cases or for purposes of investigation

Material for bacteriological diagnosis is obtained from the sputum and in the absence of sputum from throat swabs in children material aspirated from the stomach has been used Blood cultures are made as a routine where possible and cultures from urine pleural exudates and other sources obvious in the special case may be made The recovery of pneumococci in cultures may be extremely helpful where difficulty is met with in sputum typing and the determination of the absence or presence of pneumococcal bacteremia is important in directing therapy as well as in estimating the gravity of the illness In addition to the usual sputum examinations in cases with a history or evidence of chronic lung disease search should be made for tubercle bacilli and other organisms

There are several methods of determining the type of pneumococci These include the inoculation of washed sputum into a mouse precipitin tests of urine and of sputum or exudates and agglutination tests The most rapid direct and easily applied test is the Neufeld *Quellung Reaction* performed by mixing sputum on a slide with a drop of each of the several type specific sera A positive reaction consists of the swelling of the capsule of the pneumococcus on contact with the homologous type serum Rabbit serum usually is used The test can be completed in a few minutes requires but little type serum does not entail the use of animals and is as accurate as any method It can be applied to pneumo-

the oxygen concentration in inspired air is sufficiently increased the respirations are slowed and the patient becomes more quiet and often falls asleep

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of the symptoms of illness Frequently marked improvement is noted within 1 hours after treatment with a temperature approaching normal a change almost as dramatic as that of crisis in the untreated disease In other cases the temperature and symptoms subside more slowly The Francis test (for description see earlier section headed Pneumococcal Immunity) performed by the intradermal injection of the specific capsular polysaccharide in which adequate serum dosage is evidenced by a reaction at the site of injection is a valuable guide to serum administration when available By its use wasteful over-dosage can be avoided Caution is required in the interpretation of the test by reason of the occurrence of about 10 per cent of none specific reactions

Persistence of bacteremia evident spread of the lung involvement or failure of expected improvement are indications for further serum therapy Cases including those with pneumococcal endocarditis or otherwise overwhelming infections or those in whom other serious physical impairments exist contribute largely to the group in which serum therapy so far has been unavailing

In children in whom veins adequate for intravenous injection are not available the serum should be given intramuscularly in the buttocks Clinical response by this route is slower and the dose calculated by relative weights proportionally larger

Administration of Serum — Although serum is used at present very infrequently its method of use should be known If rabbit serum is used the first test dose of 2 c c previously warmed is given slowly (over at least 4 minutes) intravenously The pulse rate and blood pressure are observed carefully After 2 hours if no undesirable symptoms have appeared the remainder of the therapeutic dose provided it does not exceed 15 c c in volume may be given slowly at the rate of 2 c c per minute After 2 hours the remainder if more is calculated to be required is given slowly up to 30 c c volume If desired the therapeutic dose may be given by introducing it into an intravenous saline transfusion of 500 c c administered over a two-hour period If horse serum is used it should be given in divided doses of 5 to 10 c c at intervals of 4 hours following the initial test dose

Throughout the testing for sensitivity and the administration of serum a syringe containing epinephrine solution 1–1 000 should be at hand for immediate use in the event of anaphylactic reaction The appearance of immediate reactions is a signal for discontinuance of serum therapy Epinephrine should be given and symptoms of shock met by appropriate treatment

A thermal reaction is not uncommon after serum and is characterized by chill and rise in temperature from one half to two hours after the injection of serum and usually is not serious Some lots of sera appear to be more thermogenic others Additional causes are too rapid injections and the use of unclean paratus Later thermic reactions after 7 to 10 days are accompanied often

cocci derived from any source In order to conserve time and material, the several type sera are combined in groups upon obtaining a positive reaction with one group the process is repeated with each individual serum of that group

Sputum for typing should contain pulmonary exudate and should be collected in a clean bottle or vial to an amount preferably as much as 2 c c If some hours must elapse before the specimen can arrive at the laboratory, it may be divided into two parts, to one of which 1 0–1 5 per cent formalin is added Nasopharyngeal exudates are less reliable because they may contain in addition to the pneumococci concerned in the disease other pneumococci (often type III VI and XXII) chronically resident in the nose and throat In infants and young children nasal swabs may afford the only material available they have been used successfully by some workers Where more than one type of pneumococci is found typing should be repeated

A repetition of typing is advisable during the course of treatment especially in those cases in which rapid improvement has not followed the use of an adequate dose of serum

The type of infecting pneumococcus obviously should be determined at the earliest possible moment in order that suitable therapy may be instituted The prior use of sulfanilamide has been stated by some to interfere with type determination others have not confirmed this

DETERMINATION OF SENSITIVITY TO SERA A careful inquiry should be made to elicit a history of asthma hay fever urticaria etc and of any previous parenteral administration of foreign protein All patients should be tested for sensitivity to the serum it is contemplated to use

The ophthalmic test is made by placing one or two drops of the normal serum diluted 1 to 10 in normal salt solution into the conjunctival sac of one eye A positive reaction occurs within thirty minutes and consists of congestion of the conjunctival vessels and lacrymation with an itching and burning sensation

The skin test is performed by injecting 0 1 c c of a 1 to 100 dilution of normal serum intradermally in the forearm A positive test is indicated by the appearance within 20 minutes of an urticarial wheal surrounded by a zone of erythema

A history of asthma a positive eye test or a strongly positive skin test are contraindications to the use of serum

DOSAGE OF SERUM — The average dosage for the adult before the third day is 100 000 units in most types of pneumococcal infection In patients in whom treatment is delayed beyond the third day or who are in the upper age brackets or in whom there is multiple lobe involvement or a positive blood culture or who are in pregnancy or the puerperium the dose should be doubled

Perhaps the most reliable indications of adequate dosage are the fall in temperature and decreased pulse and respiration rates and general amelioration

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urticaria erythema and arthritis characteristic of serum sickness Epinephrine and salicylates usually will control these unpleasant symptoms

SUMMARY OF SPECIFIC TREATMENT BY SERUM —As soon as the patient is seen and the diagnosis of respiratory disease is made, sputum should be obtained for typing and culture In the absence of sputum material may be obtained from pharyngeal or other sources It is to be remembered that not infrequently definite characteristic respiratory symptoms may be absent early, and only the sudden explosive and prostrating features of the illness suggest that the disease is lobar pneumonia Here it may be better to institute treatment with a sulfonamide or penicillin rather than allow further delay in waiting for the results of later sputum examination

Inquiry is made as to a history of previous allergic disease or injections of foreign serum The eye test and intradermal skin tests are made using serum from the same animal source as that which it is proposed to use in treatment If no contraindications for the use of serum are found, the first test dose of 2 c c of type specific serum as determined by laboratory typing is given followed at intervals of two to four hours by subsequent doses as required for the calculated dose

For several hours after the initial dose of serum there is likely to be no observable change in the patient but in favorable cases especially when patients are treated early in their illness marked improvement is noted in 8 to 24 hours

TABLE III

TYPE I AND TYPE II LOBAR PNEUMONIA NUMBER OF CASES TREATED AND NOT TREATED WITH ANTISERUM AND NUMBER AND PERCENTAGE OF DEATHS BY AGE GROUP

	20–40 Years of Age			40–60 Years of Age		
	Number of Cases	Deaths		Number of Cases	Death	
		Number	Per Cent		Number	Per Cent
TYPE I						
Treated with serum	140	8	5 7	44	10	22 7
Not treated with serum	224	25	11 2	77	20	26 0
TYPE II						
Treated with serum	111	14	12 6	53	19	35 8
Not treated with serum	194	44	22 7	111	38	34 2

The acute symptoms such as dyspnea cyanosis pain and delirium are much decreased or entirely relieved The temperature drops two or three or more degrees fever may disappear entirely in the second 24 hours or persist at a low level for several days There is little change in lung as disclosed by physical examination or by x ray The lesion however does not advance In general specific serum therapy prevents or limits blood invasion, and blood cultures

previously positive often become negative in 24 hours. While it is difficult statistically *to show the effect of serum treatment on the incidence of complications* some observers have suggested that complications are decreased. Certainly the control of bacteremia should decrease the probability of metastatic lesions; on the other hand, patients seriously ill who otherwise would have died may survive to develop later complications.

The curative value of type serum varies with the type. The case fatality rate of 3,315 cases of type I pneumonia reported in the United States and Canada was 17.0 per cent; of 230 cases in Great Britain 10.4 per cent. In the Massachusetts pneumonia series the case fatality rate of 1,043 cases treated with serum was 13.9 per cent, while in 314 untreated cases (collected cases U.S. and Canada) the fatality rate was 9.0 per cent. The importance of early treatment is shown by the following: of 861 type I cases treated on the first three days 12.6 per cent died; of 18 cases treated on the fourth day 20.3 per cent died (Heffron). In the Massachusetts series of 281 type II serum treated cases 22.4 per cent died; of 1,753 collected untreated cases 37.1 per cent died. Thus far an effective antiserum from the horse for type III has not been obtained; type III serum from the rabbit seems to be moderately effective. Antisera for types V, VIII and VII and for the higher types have been studied less thoroughly, but there is an indicated reduction in case fatality following their use. Thus the case fatality of 210 type V treated cases was 16. per cent; of 154 type VII treated cases 13.0 per cent. The effect of treatment according to age and type of pneumococcus is shown in *the following table from the report of the therapeutic Trials Committee of the* Medical Research Council (Table III). The presence of bacteremia adds to the hazard of the patient with pneumonia and the case fatality rate rises; the use of serum has in general lowered case fatality rates by about 20 points in percentage (*Table IV*).

TABLE IV

TYPE I AND TYPE II LOBAR PNEUMONIA: NUMBER OF CASES TREATED WITH SPECIFIC ANTISERUM AND NUMBER AND PERCENTAGE OF DEATHS IN CASES WITH AND WITHOUT BACTEREMIA BY AGE GROUP

	0-49 Years of Age			50 Years of Age and Over		
	Number of Cases	Deaths		Number of Cases	Deaths	
		Number	Per cent		Number	Per Cent
TYPE I						
Negative	90	1	5.9	49	11	22.4
Positive	85	18	21.2	2	14	51.8
TYPE II						
Negative	87	8	9.2	5	9	36.0
Positive	34	13	38.2	13	9	69.2

urticaria, erythema and arthritis characteristic of serum sickness Epinephrine and salicylates usually will control these unpleasant symptoms

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form rashes frequent with sulfanilamide are less usual after sulfapyridine and sulfathiazole and unusual after sulfadiazine Sulfathiazole sometimes causes skin lesions resembling erythema nodosum and also conjunctivitis both of which subside on withdrawal of the drug Renal lesions arise through the precipitation of the acetylated form of the drug as crystals in the tubules of the kidney and ureters This may cause hematuria renal colic anuria and nitrogen retention They may be avoided by giving adequate amounts of fluids The use of sodium bicarbonate with the drug tends to prevent the deposit of acetylated sulfonamides in the kidney tubules The urine should be examined at frequent intervals for hematuria and crystals Gross hematuria calls for withdrawal of the drug When symptoms of hematuria or anuria occur withdrawal of the drug and the giving of abundance of water usually relieve the symptoms Lavage of the ureters and pelves of the kidneys is necessary sometimes to relieve anuria

Fever due to the drug is seen occasionally after all four of these sulfonamides When fever occurs after apparent defervescence from the original disease and during continuation of the drug in the absence of evident complications the recognition of the relation of the drug to the fever is not difficult The fever subsides shortly after the withdrawal of the medication More difficult are those cases in which there is no prolonged break in the fever curve and in which the fever from the infection shades into that caused by the drug A consideration of the clinical course of the disease determination of the concentration of the drug in the blood and withdrawal of medication usually will decide the question Less frequently the fever is accompanied by chill

Anemia has been noted after all of the sulfonamides It is more frequent after sulfanilamide and usually is a chronic secondary anemia which yields to iron and withdrawal of the drug Acute hemolytic anemia is rarer and is believed to be due to an idiosyncrasy Acute agranulocytosis also occurs occasionally usually after heavy dosage and most often after sulfanilamide A few cases have been reported following the use of sulfathiazole and sulfadiazine Thrombocytopenic purpura has been noted also after large dosage of sulfadiazine These complications are met by stopping the drug and by transfusions of whole blood

Patients who have experienced toxic reactions are likely to have them again on repetition of treatment by the drug There is some evidence that susceptibility to sulfonamides may be acquired

The effects of simultaneous administration of sulfonamides and barbiturates have been studied to determine the possibility of harm Animals receiving sulfanilamide when given doses of barbiturates such as amytal or nembutal sufficient to produce anesthesia died whereas other normal animals given the same doses of barbiturates recovered from the anesthesia without harm While serious results from simultaneous use of sulfonamides and barbiturates probably are rare the possibility of danger in man should be borne in mind

Studies of the causes of death in treated cases indicate that in many death was the result of complications such as uncontrolled bacteremia, endocarditis, empyema preexisting cardiovascular or other chronic disease or chronic alcoholism In other fatal cases insufficient or late administration of serum or the presence of mixed infections have played a part Most deaths are in patients over 50 years of age

Sulfonamides

The search for the ideal drug which would without harm to the patient destroy the infecting pneumococci or limit their growth and neutralize their toxins has been prosecuted for many years and hundreds of chemical preparations have been prepared and their effects in vitro and in vivo studied Quinine and its derivatives received much attention and of these ethylhydrocuprein (optochin) seemed most promising When used in lobar pneumonia in man, some series showed a slight reduction in case fatality rates but on the whole convincing evidence of the effectiveness of the drug was lacking and this, combined with the occurrence of serious impairment of vision in some treated cases, prevented the general use of the drug in lobar pneumonia It is still used with benefit in pneumococcal infections of the cornea

The favorable effects of sulfanilamide in infections by hemolytic streptococci in animals and in man led to the investigation of the effects of this drug in pneumococcal infections It was found to have a bacteriostatic and bactericidal effect on pneumococci in high dilutions and a definite curative effect in otherwise fatal pneumococcal infections in animals Results in pneumococcal pneumonias in man were on the whole encouraging In the past five years many derivatives of sulfanilamide have been made and tested as to their toxicity and effectiveness in combatting infections in animals and in man (see Chapter XXX–A of this volume)

Of these sulfonamides those most effective in the treatment of pneumococcal pneumonia have been sulfapyridine sulfathiazole and sulfadiazine in the order of their introduction and clinical use The nausea anorexia and vomiting which frequently accompanied the use of sulfapyridine are less with sulfathiazole and still less with sulfadiazine Other toxic manifestations vary, in part due to the differences between the drugs themselves in part to individual idiosyncrasies and to deficiencies in rates of absorption and excretion

In general the toxic reactions of the sulfonamide group are fairly frequent but usually not serious providing they are recognized promptly and measures taken to combat or avoid them The principal complications in this group are lesions of the skin of the kidney through blocking of renal tubules by deposits of acetylated crystals, agranulocytosis, anemia and drug fever Cyanosis and morbilli

until the temperature has been normal for three or four days When necessary the dosage can be increased or sodium sulfadiazine can be given intravenously

Sulfamerazine — Sulfamerazine can be used in a somewhat lower dosage one gram every 6 to 8 hours In seriously ill patients the initial intravenous dose is 4 grams of the sodium salt dissolved in a liter of physiological salt solution or in a 5 per cent solution in sterile distilled water

Solutions of the sulfonamide drugs in physiological saline solution may be given subcutaneously in concentrations of one per cent or less Although early studies suggested that renal complications following sulfadiazine were relatively rare a number of cases of hematuria and anuria have been reported often associated with low fluid intake Tolerance of the stomach to sulfadiazine favors the giving of larger doses and this together with somewhat slower excretion tend toward the establishment of higher blood levels Renal complications can be avoided to a large degree by supplying a fluid intake sufficient to maintain a daily urinary output of 1 500 c c daily examination of the urine and reduction or stopping of the drug on appearance of hematuria or oliguria

Sodium sulfapyridine sodium sulfathiazole and *sodium sulfadiazine* can be given subcutaneously also in a concentration of 3 to 5 grams to a liter of salt solution The giving of these drugs by rectal injection is unsatisfactory because of poor absorption and local irritation

Sulfathiazole and especially sulfadiazine have gained in popularity owing to their low toxicity and their effectiveness in treatment In 200 successive cases of pneumococcal pneumonia treated by sulfadiazine Flippin reported (1942) a corrected case fatality of 8 3 per cent the incidence of toxic reactions was low

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and Sulfonamides — Among the effects of type specific antipneumococ therapy are the neutralization of the toxic products of pneumococcal nd the promotion of phagocytosis by leukocytes and macrophages the lung lesion The earlier that serum becomes available the less ulation of toxic capsular material requiring neutralization The action onamides is largely bacteriostatic preventing multiplication of pneu d possibly increasing their susceptibility to phagocytosis

o types of therapy complement each other and in severe infections plish what neither could do alone The immediate availability of the without the unavoidable delay entailed by typing which must pre f serum is a great advantage to the patient Their early use may ount of serum required later The choice as to whether one or the

47

Pneumococcal pneumonia has been treated successfully with sulfapyridine sulfathiazole, sulfadiazine and more recently sulfamerazine Sulfadiazine is at the present time the most widely used by reason of its effectiveness and relative freedom from unpleasant reactions

The advantages of treatment of pneumonia by sulfonamides over that by serum are (1) the immediate availability of treatment without the delay attendant on the typing of pneumococci ( ) ease of administration and (3) greatly lessened cost of material

Sulfapyridine — The initial dose of sulfapyridine by mouth is 2 grams followed in 4 hours by 2 grams with subsequent maintenance doses of one gram every 4 hours For children the dose varies with age and should approximate 0 7 gram per 20 pounds in 24 hours This dosage will maintain a blood concentration of from 3 to 6 mgm per cent Individual variations in rates of absorption and of excretion make desirable the determination of the blood concentration from day to day In patients unable to tolerate sulfapyridine by mouth on account of nausea and vomiting or in severely ill patients or those unable to swallow or when a higher blood concentration than that obtainable by the oral route is desired, sodium sulfapyridine may be given intravenously The initial dose is 4 grams given in 5 per cent solution in distilled water (75 c c) This solution is alkaline and care should be taken to give it slowly 5 c c per minute and not to allow it to escape into the tissues outside the vein It has been found also that sodium sulfapyridine can be given orally to man with better absorption than that obtained with sulfapyridine (for other details of administration see Chapter XXX–A of this volume)

Sulfathiazole — By reason of its production of less nausea and vomiting sulfathiazole has largely replaced sulfapyridine in the treatment of pneumococcal pneumonia It is rapidly absorbed has a high anti pneumococcal efficiency and is conjugated in the blood and tissues less than is sulfapyridine It is however rapidly excreted so that sometimes it is difficult to maintain the desired blood concentration The initial dose by mouth is 4 grams followed by 1 gram every 4 hours thereafter If a blood concentration of at least 4 to 5 mgm is not attained readily an additional intravenous dose of 2 grams to 4 grams of sodium sulfathiazole can be given

Sulfadiazine — Sulfadiazine usually is well tolerated by mouth and is absorbed fairly well from the gastrointestinal tract It is excreted more slowly than is sulfathiazole The conjugation of the drug in the body usually is slight and there is no tendency for the drug to be retained in the body It will diffuse into pleural or ascitic fluid and into the subdural space in amounts from 50 to 94 per cent of the level in the blood (Peterson)

An adequate blood concentration of 6 to 9 mgm per cent as a rule is maintained easily by an initial dose of 3 grams with 1 gram every 4 hours thereafter

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Serum and Sulfonamides — Among the effects of type specific antipneumococcic serum therapy are the neutralization of the toxic products of pneumococcal growth and the promotion of phagocytosis by leukocytes and macrophages present in the lung lesion The earlier that serum becomes available the less the accumulation of toxic capsular material requiring neutralization The action of the sulfonamides is largely bacteriostatic preventing multiplication of pneumococci and possibly increasing their susceptibility to phagocytosis

The two types of therapy complement each other and in severe infections may accomplish what neither could do alone The immediate availability of the sulfonamides without the unavoidable delay entailed by typing which must precede the use of serum is a great advantage to the patient Their early use may reduce the amount of serum required later The choice as to whether one or the

other or both methods of treatment shall be used will depend on the circumstances attendant on each case

Theoretically results of combined treatment should be better than when either method is used alone but surprisingly the statistics of large series of cases are less favorable to combined treatment than to serum or sulfanilamides alone Analysis of such statistics demonstrates however that combined treatment usually has been given to patients who were seen late in the disease or who by reason of toxemia, bacteremia multiple lobe involvement complications or advanced age were evidently in grave danger Thus in the report of the Illinois Pneumonia *Control Program of 13,160 cases of pneumococcal pneumonia* (*November 1938* to July 1941) with a case fatality of 9 1 per cent, the crude death rate of cases with combined treatment was 11 0 as against 4 5 per cent with drug alone However, in one group of 666 patients showing great severity of disease i e persons over 40 with two or more lobes involved and complications present 546 were given combined treatment and 120 were given drug treatment only Other classifications similarly indicate a selection of patients for combined therapy from those most seriously ill Of 3 604 patients without complications or associated diseases, who received combined treatment the case fatality rate was 3 8 per cent of a similar category of 2 839 patients treated with drug alone the rate was 1 9 per cent

The favorable effects of a state wide pneumonia control program are shown in Table V

TABLE V

PNEUMONIA IN ILLINOIS 1935–1941

Year	*Cases reported*	*Deaths*	*Fatality rate**
1935	13 519	5 984	44 3
1936	15 926	6 31[illegible]	39 6
1937	14 970	5 512	36 8
1938	1[illegible] 834	4 595	35 8
Illinois Pneumonia Control Program inaugurated November 1938			
1939	13 472	4 1[illegible]3	31 1
1940	14 59	3 738	[illegible]5 6
Jan 1 1939–June 30 1939	1 448	222	15 3
July 1 1939–June 30 1940	6 348	539	8 5
July 1 1940–June 30 1941	7 652	664	8 7

*Per hundred cases reported

A similar program using penicillin should show even better results

All patients should receive complete bacteriological study and where sulfonamides are used adequate studies of blood and urine before and during treatment

Penicillin

Penicillin obtained from the growth of the mould *Penicillium notatum* is an unstable acid which is supplied as the sodium or calcium salt Its potency is expressed in Oxford units an arbitrary amount determined by comparison with standard preparations It is estimated that pure penicillin would have a potency of 1 000 units per milligram the serious losses of active substance in the attainment of high degrees of purity did not warrant insistence on so great refinement and most preparations are accepted with less potency 100 units per milligram having been regarded as acceptable for clinical use Penicillin even in low concentrations has a bacteriostatic and possibly bactericidal action on certain species of bacteria Most of these bacterial species are gram positive and include the pneumococcus staphylococcus and streptococcus pyogenes as well as certain gram positive bacillary forms The gonococcus and meningococcus also are susceptible

In the treatment of pneumonia penicillin is best administered parenterally either subcutaneously intramuscularly or intravenously It is excreted rapidly in the urine and to maintain a continuingly effective blood level it is necessary to repeat the subcutaneous or intramuscular injections every 3 hours or to employ continuous intravenous injection Total daily dosage of 120 000 units is employed usually Various methods of slowing the local absorption of penicillin by the admixture of oils or waxes have been devised to reduce the frequency of injections to every 6 to 8 hours

Penicillin is destroyed rapidly by acid and by gross bacterial action in the colon so that it is not effective in its ordinary state when given by mouth or rectum Preparations for oral use in which the penicillin is protected from gastric acid are available now but in most cases of pneumonia the emergency is met best by parenteral methods

Other Treatment

Treatment by *pneumothorax* has been employed in selected cases of lobar pneumonia for the relief of pleural pain Clinical improvement characterized by slowing of respirations relief of cyanosis and reduction in temperature was noted in some cases following pneumothorax but this treatment has not gained general acceptance The relief of cyanosis with slowing of respirations following pneumothorax is of considerable theoretical interest tending to support the contention that rapid shallow breathing is a large factor in the production of cyanosis in lobar pneumonia

Many studies have been made of the effects of the *parenteral use of vaccines* derived from pneumococci on the course of pneumonia It has been claimed that the development of immune bodies is hastened and that therefore vaccines

other or both methods of treatment shall be used will depend on the circumstances attendant on each case

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Some effort has been directed toward the control of acute lobar pneumonia the most widespread and serious of the respiratory diseases and while the measures devised have sometimes been effective in cutting short local epidemics and in the prevention of the disease in individuals the incidence of pneumonia in the general population over periods of years has not been reduced materially The pneumococcus is widespread among the healthy as well as the sick and opportunities for the transfer of organisms from one person to another in the close contacts of daily life especially in cities are so numerous that the effective control of pneumonia has appeared almost hopeless

The contagious character of pneumonia is now recognized as a large factor in the spread of the disease and many cases of pneumonia whose origin hitherto was unexplainable can now be shown by appropriate methods to have resulted from contacts with other cases Intelligent isolation of the pneumonia patient will prevent to a large extent infections from this source and help to reduce morbidity from the disease The demonstration of the relatively low virulence of the pneumococci commonly found in the mouths of healthy persons and their differentiation from the other more virulent types of pneumococci found in the majority of the severe pneumonias together with the frequent history of predisposing factors as fatigue or wetting in those who develop pneumonia due to these less virulent organisms help to clarify the relation of contagion on the one hand and predisposing physical factors on the other in the causation of pneumonia

In a few instances pneumococci found in healthy persons belong to the more virulent types and often such persons are found to have been in contact with cases of pneumonia Those in attendance on patients with pneumonia exhibit a much larger proportion of virulent organisms in their throats than other persons not in such close contact Persons convalescent from pneumonia may harbor virulent pneumococci for many days although in some cases the virulent are replaced by avirulent strains of different type very early in convalescence The extent to which healthy carriers of virulent pneumococci participate in the spread of pneumonia still is undetermined

Measures taken for the prevention of pneumonia evidently are to be directed toward the establishment of favorable hygienic conditions in the community and toward the protection of the individual from infection Education will prove more effective than ordinances Of the general measures the proper ventilation and cleaning of buildings and public conveyances the prevention of promiscuous expectoration and the prevention of overcrowding in public gatherings and in institutions are important

In asylums jails lodging houses and hospitals the prompt isolation of the first cases of pneumonia and the partial isolation of the healthy by screening the beds in dormitories or hospital wards thus placing each person in a separate cubicle

should be helpful A critical review of results indicates that vaccines used in the treatment of lobar pneumonia are of little or no value

In some cases especially those in which resolution is delayed, *treatment by x ray* and by the inductotherm has been used sometimes with apparent benefit

Polysaccharide splitting Enzymes — The effect of enzymes derived from other bacteria on the capsular material of pneumococci is of biological and theoretical interest In view of the evident relation of capsular substance of the pneumococci to toxemia and to resistance by the organism to phagocytosis Avery and Dubos inaugurated a systematic search for some ferment which would break down the polysaccharide of the pneumococcal capsule After long search they isolated from a mixed bacterial suspension, derived from soil from a peat bog a bacillus (S III bacillus) which when grown on a suitable mineral medium is able to elaborate a heat labile enzyme capable of decomposing the polysaccharide of the capsule of pneumococcus type III This enzyme has no effect on the polysaccharides of types I or II Pneumococcus type III, when exposed to this enzyme loses its capsule but continues to grow and when transferred to a medium containing no enzyme reacquires its capsule

The action of the enzyme is neither bacteriostatic bactericidal nor bacteriolytic it decomposes the capsular substance without inhibiting its production The organism thus deprived of its capsule becomes susceptible to phagocytosis It was then found that a small amount of the enzyme would protect mice against a million fatal doses of virulent type III pneumococci and had a curative action in mice when given 18 hours after infection

Finally in monkeys infected with type III pneumococci and treated with the enzyme extension of the pneumonic process was limited sterilization of the blood was promoted, and the case fatality reduced Sickles and Shaw found a soil bacillus which produces an enzyme specific for the polysaccharide of type II pneumococcus another with similar effects on type VIII and still another effective to some degree on the capsular material of type I pneumococci

These discoveries, while not immediately applicable to the treatment of pneumonia in man are of great biological significance and offer the possibility of a new therapeutic approach in the treatment of infectious disease

PROPHYLAXIS

Sanitary measures devised for the prevention of acute respiratory disease have been far less successful than those directed toward the control of gastrointestinal diseases Infection by direct transfer of organisms from the sick to the well through coughing and close contact is more difficult of prevention than infection which occurs by indirect means as in food and water in the gastrointestinal infections

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The contagious character of pneumonia is now recognized as a large factor in the spread of the disease and many cases of pneumonia whose origin hitherto was unexplainable can now be shown by appropriate methods to have resulted from contacts with other cases Intelligent isolation of the pneumonia patient will prevent to a large extent infections from this source and help to reduce morbidity from the disease The demonstration of the relatively low virulence of the pneumococci commonly found in the mouths of healthy persons and their differentiation from the other more virulent types of pneumococci found in the majority of the severe pneumonias together with the frequent history of predisposing factors as fatigue or wetting in those who develop pneumonia due to these less virulent organisms helps to clarify the relation of contagion on the one hand and predisposing physical factors on the other in the causation of pneumonia

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The contagious character of pneumonia is now recognized as a large factor in the spread of the disease and many cases of pneumonia whose origin hitherto was unexplainable can now be shown by appropriate methods to have resulted from contacts with other cases Intelligent isolation of the pneumonia patient will prevent to a large extent infections from this source and help to reduce morbidity from the disease The demonstration of the relatively low virulence of the pneumococci commonly found in the mouths of healthy persons and their differentiation from the other more virulent types of pneumococci found in the majority of the severe pneumonias together with the frequent history of predisposing factors as fatigue or wetting in those who develop pneumonia due to these less virulent organisms help to clarify the relation of contagion on the one hand and predisposing physical factors on the other in the causation of pneumonia

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In asylums jails lodging houses and hospitals the prompt isolation of the first cases of pneumonia and the partial isolation of the healthy by screening the beds in dormitories or hospital wards thus placing each person in a separate cubicle

will hinder the spread of infection by coughing and sneezing and go far toward preventing an epidemic

The individual may do much for himself in preventing pneumonia Fifty per cent of patients with pneumonia give a history of coughs and colds preceding by several days the onset of the more severe illness and in many of these it is probable that rest and avoidance of further exposure would have enabled them to resist the more serious pneumococcal invasion The efficacy of the hot bath and subsequent rest in bed following exposure to wet and cold remains unchallenged as a preventive of respiratory infections The correction of defects in the noses and throats of children and the maintenance of oral cleanliness all contribute to freedom from respiratory disease Dissipation overwork underfeeding and irregularities in food and hours of rest all tend to decrease resistance to infection and hence are to be avoided Persons differ widely in the amount of exercise required to keep them fit but sufficient exercise should be taken to maintain the appetite, regulate bodily functions and along with proper food intake to avoid the acquisition of fat in excess of that which is usual for the person in question Unnecessary exposure to those sick with pneumonia is to be avoided for in over 60 per cent of cases the infection is likely to be due to one of the virulent types of pneumococci against which the resistance of the body may not be sufficient to prevent invasion

Isolation of the patient care of the sputum and disinfection of articles coming in contact with him will protect members of the family and others from infection The use of face masks by nurses and attendants undoubtedly diminishes the likelihood that pneumococci discharged into the air by the coughing of the patient will be drawn into the mouths of those about him The prevention of dust by the removal of superfluous rugs and hangings from the sick room and the frequent wiping of the floor and furniture with a moist cloth will reduce the danger of infection by dust particles which may carry virulent pneumococci In World War II the prevention of respiratory infections in troops was restudied under the Respiratory Disease Commission O H Robertson and his associates found that environmental contamination by infective material from diseased persons which resulted in the distribution of particulate matter in the air from dry sweeping and bed making was more important in spreading disease than 'droplet nuclei' direct from patients The application of oil to floors and blankets reduced the incidence of respiratory infection including pneumonia Triethylene glycol vapor was employed also as a disinfecting agent The frequent washing of the hands of attendants after handling the patient is important in preventing the inadvertent transfer of organisms to the mouth A room that has been occupied by a pneumonia patient should be cleaned thoroughly and the bedding disinfected Soap and water heat and exposure to sunlight and fresh air are still the most readily obtainable and effective agents at our disposal Disin

fection of mattresses and bedding in a steam sterilizer is perhaps the surest and quickest method where the apparatus is available Disinfectants relatively harmless to fabrics may be used in cleaning but the destruction of infection is largely a matter of mechanical removal

Prophylaxis by Sulfadiazine — Coburn reported the prophylactic treatment of respiratory infections of 600 000 naval personnel with sulfadiazine in two daily doses of 1 0 gm or of 0 5 gm The incidence of pneumococcal pneumonia was lowered significantly by this at most naval stations

Prophylactic Vaccination — Prophylactic immunization against pneumococcal infection has not attained the importance among methods devised for the control of respiratory disease that has been achieved by antityphoid vaccination in the prevention of typhoid fever but despite the obstacles in the way of its practical application at present more may be accomplished in the future

The multiplicity of types of pneumococci adds to the difficulties of successful immunization and of the evaluation of the results attained thereby In the present state of knowledge it seems likely that attempts at the immunization of uncontrolled shifting populations of civil communities will result in but little definite benefit and that efforts at other means of control such as the isolation of patients will prove more effective in reducing respiratory disease But where the persons of a community are more restricted in their movements and in closer reciprocal contact as in prisons hospitals asylums boarding schools or in military camps prophylactic immunization may be considered as a means of control of pneumonia particularly during epidemics due to known types of pneumococci

It is now established that the injection of dead pneumococci in doses of permissible size will produce immunity in man as well as in animals and that the serum of persons so inoculated contains immune bodies such as agglutinins opsonins and protective substances in quantities demonstrable by appropriate methods The duration of this immunity still is undetermined although there is evidence that it may last eight or nine months or perhaps longer It has been found also that the blood of 35 per cent of normal persons contains antipneumococcal substances which presumably contribute to their protection against pneumococcal infection

The first extensive attempt at prophylactic immunization against pneumonia was made in 1911–1912 by Sir A E Wright in the Rand Mines where lobar pneumonia causes a high death rate among native workers The interpretation of the results of this pioneer work was made difficult by the absence of type determinations which subsequently have been found essential in any study of pneumococcal immunity The South African studies were continued by F S Lister who differentiated pneumococci into types and independently submitted a classification similar to that of Dochez and Gillespie Lister inoculated workers in the Crown Premier Diamond and De Beers Diamond Mines with vaccines containing

the prevailing types of pneumococci types A B and C The vaccine contained two billions of each type per dose Three doses were given subcutaneously at intervals of seven days The vaccinated miners were observed for a period of six to twelve months and in all three mines a definite decrease in the incidence and mortality from pneumonia was observed At the Crown Mines the type of pneumococcus in every case of pneumonia which occurred among vaccinated men was determined and no cases were found of the types vaccinated against over a period of nine months Lister laid stress on the probability that the protection of a considerable part of the community by inoculation lessens the number of carriers and perhaps the virulence of the strains found in the community and hence confers a definite benefit upon the uninoculated group This would affect in a statistical sense the use of the uninoculated group as controls

Cecil and Austin reported the results of the prophylactic inoculation against pneumonia of 12 510 men at Camp Upton in 1918 A preliminary study of the first 100 cases of pneumonia had shown that about 70 per cent were caused by types I II or III The vaccine was given subcutaneously in four doses of 0 5 c c each The first dose contained one billion each of types I, II and III, the second dose two billion of each and the third and fourth doses three billion of each of types I and II and one and one half billion of type III The majority of the men received three or four inoculations usually at intervals of five to seven days Severe reactions were unusual and it was the opinion of the regimental surgeons that the reactions were milder than those following typhoid vaccination A study of agglutinins and protective power of the serum of 42 persons vaccinated against types I II and III showed a definite immune response to types I and II but little response to type III

During the ten weeks ensuing after vaccination there were no cases of pneumonia due to types I II and III among 12 519 men whereas among 20 000 unvaccinated in the same camp there were 6 cases There were only 6 cases of group IV pneumonia among the men who received two or more inoculations of vaccine whereas there were 33 cases among the unvaccinated troops Still more interesting is the observation that while among the unvaccinated troops there were 106 cases of streptococcus pneumonia only 6 cases occurred among the vaccinated Among 3 500 colored troops half the companies were vaccinated *the other half not There were 28 cases of streptococcus pneumonia among the* unvaccinated and only cases among the vaccinated yet these men were living in the same part of the camp and closely associated on the drill grounds and in recreation and amusement halls Cecil and Austin offered no explanation for this observed fact The death rate from pneumonia during the ten weeks of observation was 0 83 per 1,000 for the vaccinated and 12 8 per 1 000 for the unvaccinated men

At Camp Wheeler 13 460 men were vaccinated with a lipovaccine containing

ten billion each of types I II and III and most of these troops were under observation for two to three months after vaccination The results of vaccinations which began September 1918 were not so striking at Camp Wheeler as at Camp Upton largely on account of the influenza epidemic demobilization cut short the observations in December The effect of vaccination was most evident in seasoned men among whom the pneumonia incidence rate per 1 000 men was 7 2 per cent for vaccinated men and 46 4 per cent for unvaccinated During the period of observation there were 32 cases of types I II and III pneumonia among the vaccinated four fifths of the camp and 4 cases among the unvaccinated one fifth If the fact that the serological evidence of immunity is obtainable only after a period of eight days following vaccination is taken into account and all cases of pneumonia occurring within one week of vaccination are excluded there remain only 8 cases of pneumonia due to the fixed types vaccinated against and these all followed severe influenzal infection The mortality rate for primary pneumonia among vaccinated troops was 11 9 per cent and for unvaccinated 31 8 per cent On the other hand the mortality rate in pneumonia secondary to influenza was about the same for vaccinated and unvaccinated groups

A number of family and institutional outbreaks of pneumonia have been studied and in a few attempts at control by vaccination have been reported Smillie in 1936 vaccinated 630 inmates and attendants in an insane hospital in which type II pneumonia was occurring Thirty carriers of type II pneumococcus were found Before vaccination there had occurred 17 cases of type II pneumonia There were no further cases of pneumonia after vaccination although a number of vaccinated persons continued to harbor type II *pneumococci* The results appeared to be significant but the number of vaccinated persons was too small to admit of unqualified conclusions Immunization of residents in camps of young men enrolled in the Civilian Conservation Corps using chemical derivatives of type I and type II pneumococci has been carried on by Felton with encouraging results

Kaufman treated a group of persons in an old people s home with an antigen of the capsular polysaccharide derived from cultures of pneumococcus types I and II There was a reduction in the incidence of pneumonia in the inoculated as compared with the control group

MacLeod and associates immunized soldiers in an Army Air Force Technical School World War II with 0 03 to 0 06 mgm each of the capsular polysaccharides of pneumococcus types I II V and VII given by a single subcutaneous injection They found this treatment effective in preventing pneumonia caused by these types but not that due to heterologous types Evidence of immunity appeared within a period of 2 weeks its duration was not determined it was believed to last for a minimum of six months The carrier rate for these types was reduced in the immunized as compared with the control group

Prophylactic vaccination under the conditions of these mass experiments appears to have been effective to a considerable degree in prevention of pneumonia of the known types, and the results justify the hope that the method may be a valuable adjunct to other preventive methods in the control of epidemics in small compact civil communities It is hardly necessary to remark that in the interest of scientific medicine as well as on practical grounds where routine immunization is contemplated adequate studies of types of pneumococci should be made Furthermore where prophylactic inoculation is practised, whether in the attempted control of local epidemics or for the protection of individuals the anticipated protection from vaccination should not be emphasized to the exclusion of well recognized methods of hygiene of the community and of the individual

At best the protection is relative only and in so far as concerns the individual, apparently is confined to specific types of pneumococci used in immunization

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CHAPTER XXVIII-A

HEMOLYTIC STREPTOCOCCUS PNEUMONIA

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The hemolytic streptococcus is the most frequent of the bacterial agents responsible for the pneumonias which were formerly called bronchopneumonia and which now are included under the general classification of atypical pneumonias. In its application to the hemolytic streptococcus pneumonias however the term atypical refers only to the clinical course and anatomical lesion as they compare with those of the classical lobar pneumonias caused by the pneumococcus. Cases of hemolytic streptococcus pneumonia usually exhibit a characteristic clinical course which makes it possible to distinguish them clinically. They have been encountered most frequently as the serious complications of measles and influenza and during epidemics of the latter diseases the prevalence of hemolytic streptococcus pneumonia may assume epidemic proportions as a primary disease even among persons not afflicted with measles or influenza.

Historical Review

To Finkler[1] belongs the credit for establishing streptococcus pneumonia as a specific disease entity with distinctive clinical and pathological features Be fore the Deutsch Kongress fur innere Medizin in 1888 he presented a classifica tion of pneumonias which he divided into the typical forms and those having an atypical course The latter he subdivided into those which are primary and those which are secondary to or associated with other illnesses Among the atypical forms he included several groups each having an essentially peculiar type of illness In the following year before the same congress Finkler reported the constant finding of streptococci indistinguishable from *Streptococcus erysipelatis* in one of the groups of atypical pneumonias in which there was a toxic or typhoid like course and to which he now applied the term primary streptococcus pneumonia

The cases which he described were mostly secondary and less often primary They had such a similar course and symptoms that he felt probably they could be diagnosed during life Pathologically they presented often multiple lobular lesions and often a confluent bronchopneumonia The fact that the disease showed no clean cut termination was explained by the involvement of the lung parenchyma Finkler used the term acute interstitial pneumonia, to describe the pulmonary lesion He recognized both the malignant and the contagious character of the disease having described an outbreak during the previous year in which there were 6 related cases with 3 deaths and having encountered other groups of cases with similar pathological findings in the intervening months In all the cases that were examined at autopsy the streptococcus was found as the only organism except in 1 case which yielded a staphylococcus in addition He pointed out the similarity of these cases to other pneumonias occurring in ani mals and felt that the lesion was essentially an erysipelas of the lung

During the ensuing year there occurred the great pandemic of influenza of 1889–90 In that epidemic Finkler saw 45 cases of the so called influenzal pneu monia Two of them were typical cases of lobar pneumonia and the rest were like the streptococcus pneumonias that he had described Among them were a number of rapidly fatal cases in which he observed a splenization of the lung In these cases he found the streptococcus in the sputum and in the lung juice obtained by puncture during life as well as in the lungs at autopsy

The pathology of the latter cases was described in two papers by Ribbert, who also recounted the reports of a number of other authors who had found streptococci in cases of pneumonia and influenza Finkler made little mention of empyema in his cases but Ribbert in his second paper reported the finding of empyema during life and at autopsy in patients who had suffered from severe

streptococcus pneumonia during the influenza epidemic several weeks previously. In some of the cases he observed that the trachea and bronchi were red and swollen and occasional patients developed metastatic lesions in bones and joints. Streptococci were identified in most of the infected exudates.

Descriptions of cases with pathological features similar to those of streptococcus pneumonia but without identification of the causative organism are given in earlier writings of Delafield and among the autopsy protocols of soldiers who died during the Civil War[4]. The latter are of particular interest since in 101 of the 135 autopsies of cases of so called secondary or catarrhal inflammation of the lungs the condition was associated with measles. Pleurisy with effusion was frequent in these cases and pericarditis occurred in a few. MacCallum obtained some of these specimens which had been preserved in the Army Medical Museum and made freshly stained sections from them. In these sections he recognized changes similar to those of streptococcus bronchopneumonia with necrosis and actually observed chains of cocci in the alveoli.

Other authors notably Netter[6], Weichselbaum[7] and Wassermann found streptococci either alone or with other organisms in cases of bronchopneumonia as well as in empyema. In more recent years Mathers[9] described a number of cases of atypical pneumonia occurring during 1915–16 in conjunction with an epidemic of influenza that occurred in Chicago. His cases were similar to those described by Ribbert. He also noted extensive hemopurulent pleuritis and sometimes pericarditis. The hemolytic streptococcus was the most frequent organism obtained from these cases. This author also described an almost simultaneous outbreak of horse distemper at the Union Stock Yards Veterinary Hospital in which autopsies in over 100 animals revealed similar pathological findings in the lungs and hemolytic streptococci either in pure or in mixed cultures were found regularly. A large percentage of the animals had positive blood cultures during life and the organisms were obtained also from lung punctures and from infected foci. These streptococci differed from the human strains.

Considerably larger numbers of cases of streptococcus pneumonia and empyema were recognized and described during World War I in 1917 to 1919. These occurred chiefly in army camps first as complications of measles and subsequently during the pandemic of influenza. The clinical and pathological features of these cases were recorded in detail by a number of workers[1] particularly by MacCallum[1].

Occurrence and Epidemiology

The exact incidence of hemolytic streptococcus pneumonia is difficult to determine. Much depends on the sources of material and the extent to which the bacteriological studies are carried. Etiological studies based on autopsy

material alone while quite reliable in general are subject to the criticism that they are obtained from a selected group of cases namely, the fatal ones In addition one cannot always exclude the possibility that the bacteria found at autopsy may represent partly or entirely invaders which are either secondary or terminal Studies based on clinical material are subject to numerous difficulties Even under the best conditions it is difficult to exclude contamination from the upper respiratory tract especially in sputum studies Data based on lung punctures made during life are of course highly reliable but this method of obtaining cultures has been used rarely in cases of atypical pneumonia The etiological data obtained from most clinics and laboratories furthermore, often are incomplete because the methods used at least in recent years, have been designed chiefly for the purpose of determining pneumococcus types or of excluding the presence of pneumococci Under these conditions other bacteria are noted only if they are unusually prevalent or if they appear in pure culture in the specimens examined Seasonal variations and the occurrence of periods of epidemic prevalence must be considered also These and other difficulties will suffice to explain the great divergences in incidence of streptococcus pneumonia recorded by different observers Usually it is necessary to qualify such information with respect to its source the time when it was collected and the type of material upon which it is based

Among 700 cases of atypical pneumonia collected from the world literature by Reimann[1] 24 per cent were caused by the streptococcus Except for Cole s series[13] which was included among these 700 cases, the cultures were made from the lungs at autopsy in all instances In Cole s 211 cases of primary atypical pneumonia in adults which were admitted to the Hospital of the Rockefeller Institute from 1911 to 1927 39 per cent were considered to be due to the hemolytic streptococcus because these organisms were found in predominating numbers in sputum or were isolated from pleural exudate or from the lungs and blood postmortem More than one half of these cases were seen during the 1917–18 season when streptococcus pneumonias were unusually prevalent elsewhere as a complication of measles At the Harlem Hospital from 1928 to 1936 Bullowa[14] made bacteriological studies in 6 128 cases of all kinds of pneumonia in all age groups and found beta hemolytic streptococci as the predominant organisms in 2 8 per cent of the cases Among children the incidence was 3 4 per cent in those under 2 years and 4 7 per cent in those over 2 while in adults the incidence was 2 4 per cent Rumreich[15] of the United States Public Health Service together with other workers collected 25 80 cases in a nation wide survey of the bacterial etiology of all kinds of pneumonia over a 2 year period ending September, 1940 They found hemolytic streptococcus as the only or predominant organism in - 65 per cent of their cases Among those classified as lobar pneu

monia the incidence was 2 00 per cent as compared with 3 33 per cent among th bronchopneumonias In a more circumscribed study based on a survey of ,791 cases in which sputum was submitted to the New York City laboratory for bac teriological study during a 6 month period Lawrence and Sutliff [6] encountered 126 cases of pneumonia in which hemolytic streptococci comprised more than 15 per cent of the organisms obtained in the cultures In 45 of these cases pneumo cocci were found in addition

The incidence of streptococcus pneumonia in infants and children also shows wide variations In Trask s series[17] of 668 cases of pneumonia empyema and bronchitis in children admitted to the New Haven Hospital between 1927 and 1933 36 or 5 4 per cent were considered to be due to hemolytic streptococcus pneumonias These included 21 of the 94 deaths in the entire series and hemo lytic streptococci were obtained in postmortem cultures in 8 additional cases which were not classified clinically as streptococcus pneumonia In Lyon s series [9] of 165 cases of pneumonia and empyema in infants and children at the Boston City Hospital hemolytic streptococci were considered causative in 1 of the 98 cases of lobar pneumonia in 8 of the 52 cases of bronchopneumonia and in 4 of the 37 cases of empyema Menten Bailey and DeBone in a study of 131 autopsies at the Children s Hospital in Pittsburgh found hemolytic streptococci alone in 10 cases and mixed with other organisms in 1 additional cases these organisms being obtained directly from the consolidated lungs

Hemolytic streptococci usually are more prevalent in cases of empyema than in all pneumonias This is due partly to the fact that hemolytic streptococcus empyemas not infrequently are found in the super infections of cases of pneumo coccus pneumonia but also because of the high incidence of this complication in the primary streptococcus pneumonias Netter found streptococci alone in 51 of 109 purulent pleural effusions At the Boston City Hospital Locke found 88 cases of hemolytic streptococcus empyema among 478 cases observed over a period of 7 years an incidence of 18.4 per cent Of the cases of massive empyema about 75 per cent were due to hemolytic streptococci Nowak in a later series of empyemas from the same hospital found hemolytic streptococci alone in 15 6 per cent and mixed with staphylococcus aureus in an additional 2 8 per cent In Lanman and Heyl s series of 287 cases of empyema occurring at the Chil dren s Hospital in Boston over a 10 year period 10 4 per cent yielded hemolytic streptococci as the predominant organisms

The pneumonias complicating measles are predominantly streptococcus pneu monias This was shown very strikingly in the United States Army Camps during 1917 and 1918 (Clendening [4] Opie and associates Cole and MacCal lum Miller and Lusk [7] Irons and Marine [9] Hamburger and associates [9]) At Camp Zachary Taylor Hamburger and Mayers [9] found hemolytic streptococci

mostly in pure culture in 52 of 93 cases During the influenza epidemic at Camp Wadsworth North Carolina Birge and Havens[30] cultured hemolytic streptococci from heart s blood lungs or both in 60 of 118 cases of pneumonia complicating this infection Numerous other writers have noted the regular or frequent occurrence of hemolytic streptococcus pneumonia as a complication of influenza

Opie and associates and Cole and MacCallum demonstrated the rapid spread of hemolytic streptococcus respiratory infections in hospital wards where patients with pneumococcus pneumonia are nursed This accounted for many of the hemolytic streptococci that were obtained from lungs and heart s blood in the autopsies done during the outbreaks that were studied at that time Person to person spread of streptococcus pneumonia had been observed by Finkler[1b] as already noted In general epidemics of streptococcus pneumonia are circumscribed and usually limited to households hospital wards or army camps, even when they occur in conjunction with outbreaks of measles or influenza

Etiology

The organisms associated with streptococcus pneumonia were identified in the early reports as *Streptococcus pyogenes* or *Streptococcus erysipelatis*[1] Since then they have been recognized as beta hemolytic streptococci Those strains, which have been studied by recent serological methods have all been found to belong to Group A (Bowert Keefer and associates) Keefer succeeded in typing 32 of 55 strains from as many patients with streptococcus pneumonia at the Boston City Hospital Of these 32 strains 15 showed cross reactions with types XV and XVII sera and the 17 other strains belonged to 6 of the other Griffith agglutinative types

Many cases of pneumonia have been reported in which the only or predominant organism is a non hemolytic streptococcus or more often a *Streptococcus viridans* (Calmels[3] Senerchia and Livengood[4]) Since these organisms usually are found in abundance in the nasopharynx and sputum of normal individuals their relation to pneumonia is open to grave doubt Some of the cases reported by Senerchia and Livengood [4] which failed to respond to sulfapyridine therapy may fall into the category of cases of atypical pneumonia of unknown etiology in which some form of virus as yet unrecognized may be the inciting cause Certainly the non hemolytic streptococci and *Streptococcus viridans* have been predominant in cultures made in such cases Furthermore it is not always possible to rely on the type of hemolysis on the surface of blood agar plates to differentiate the various forms of streptococci nor is it always possible to differentiate *Streptococcus viridans* from pneumococcus without careful tests for bile solubility

Five of Trask s cases had a scarlatiniform rash In each of 3 of these cases Trask and Blake[35] were able to demonstrate the presence of a toxin with the general properties of the Dick scarlet fever toxin However, the two toxins were quite different in their neutralizing reaction An antitoxin effective against one was not necessarily effective against the other

Predisposing Factors

Streptococcus pneumonia usually follows some other infection involving the respiratory tract In addition to measles and influenza, which are by far the most frequent antecedents particularly during epidemics, the disease may follow scarlet fever or other streptococcus sore throats the common cold or less frequently whooping cough When it occurs after the common cold or after a simple nasopharyngitis the pneumonia usually is considered to be primary By the same token it may be proper to consider the streptococcus pneumonias that follow measles and influenza as primary although usually they are referred to in connection with the antecedent illness as a measles pneumonia or influenzal pneumonia While one of these types of respiratory infection usually precedes the onset of primary streptococcus pneumonia it may occur without any apparent antecedent illness[36] In Sharp s series[37] all but 1 of 17 cases of the so called bronchogenic type were preceded by some outstanding primary illness After focal streptococcal infections or as part of hemolytic streptococcus septicemias metastatic involvement of the lung may occur or a streptococcus pneumonia may be a terminal event in patients with severe debilitating diseases The hemolytic streptococcus is also the most common of the organisms which give rise to reinfection in cases of pneumococcus lobar pneumonia[14,24,25,38] Finkler[1] and Sharp[37] as well as others have encountered cases which had a subacute or chronic course and which proved to have underlying pulmonary tuberculosis

Streptococcus pneumonia occurs at all ages It is somewhat more frequent in infants and children under 2 years of age than in older children [7] Like other primary pneumonias it is more common in males than in females usually in a ratio of about 3 to 2 According to Cecil[19] and Miller and Lusk[21] negroes are more susceptible than whites although fewer of the former develop empyema

Pathogenesis

Sharp[37] classified 17 of 23 cases of endemic streptococcus pneumonia which occurred at the New Haven Hospital as bronchogenic The remaining cases which were all incidental to known blood stream infections were called hematogenous although the distinction was difficult to make in individual cases These 6

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cases of hematogenous streptococcus pneumonia occurred among 63 patients with hemolytic streptococcus septicemia that were observed during the same period Keefer and associates[40a] observed metastatic pneumonia in 7 3 per cent of 246 cases of hemolytic streptococcus bacteremia at the Boston City Hospital and Schwartzman and Goldman[40b] noted it in 8 of 168 cases of hemolytic streptococcus septicemia at Mount Sinai Hospital New York Netter[6b] suggested that all bronchopneumonias are caused by agents which come from the mouth and are therefore superinfections occurring after other contagious diseases The hemolytic streptococcus itself while frequently associated with pharyngitis, tonsillitis and sinusitis, seldom is invasive enough under these circumstances to produce pneumonia During the course of certain infections notably measles and influenza there appears to be a local loss of resistance which permits the streptococcus to penetrate and to spread to the trachea and bronchi The rich lymphatic supply in this region permits the organisms to spread to the regional lymph nodes and the interstitial tissue of the lungs Reimann[1] suggested that the tendency of this type of infection to spread may be due in part to the ability of the hemolytic streptococcus to delay the coagulation of plasma or exudate and to dissolve fibrin

Pathology

Descriptions of the pathology of streptococcus pneumonia have been given by Finkler[1] Ribbert Mathers[9] MacCallum[3 11d] Glomset[41] Cole[13] and Menten and associates[19] Many of the descriptions are from cases which occurred as complications of measles and influenza in the United States Army Camps and have been collected by Callender[10]

The inflammatory reaction involves the larynx trachea and entire bronchial tree as well as the lung The mucous membrane of the larynx trachea and bronchi exhibits a characteristic dark red color which may be due to the laking of blood There is usually intense hyperemia and even hemorrhage in these structures and there may be actual necrosis of the thyroid cartilage arytenoids and bronchial walls and occasionally destruction of the epiglottis and vocal cords The severest reactions have been observed in very acute cases especially in those complicating measles

Two main types of pulmonary lesions have been described by MacCallum[3] although frequently they may occur together The first which he and others have designated as interstitial bronchopneumonia is essentially a bronchiolitis with extension to the adjacent pulmonary tissue The bronchi are markedly thickened both because of the hyperemia and also because of an additional infiltration with mononuclear cells This thickening is accompanied by a patchy atelectasis resulting from obstruction of the bronchioles and giving rise to a nodular

type of consolidation There is also extreme engorgement of the blood vessels with hemorrhages about these nodules of consolidation The alveolar walls like those of the bronchi become infiltrated with mononuclear cells the capillaries become distended and the epithelium proliferates rapidly and desquamates The alveolar spaces in the neighborhood of the bronchi then become filled with blood dense fibrin and a few mononuclears The more distant alveoli contain fewer cells but often are filled with thick viscid fluid which may give even enough of an appearance of confluence to give the gross appearance of a lobar pneumonia Usually however there are large areas of intervening air-containing alveoli Streptococci may be found in tangled masses in the lumen of the bronchi or bronchioles mingled with the leucocytic exudate but they are relatively infrequent in the bronchial walls or in the alveolar exudate

According to MacCallum[5] the streptococcus spreads by way of the lymphatics which run from the pleural network along the interlobar septa bronchial walls and blood vessel walls to the hilar nodes Many streptococci are found in these lymph channels and in the sinuses of the hilar lymph nodes The former become thrombosed and markedly distended reaching a diameter of 2 to 3 millimeters and become quite conspicuous because of their yellowish white content They may be confused sometimes with small obstructed bronchioles He believes that the bacteria extend by growing along the obstructed lymph channels in both directions and thus pass from the lung to the pleura setting up an inflammation with an outpouring of a fluid exudate The pleura itself and all the interlobar septa become edematous and permeated with a serofibrinous exudate containing wandering cells Pleural effusion begins very early progresses with extreme rapidity and soon becomes a dominant feature When extremely large quantities of fluid accumulate in one of the pleural cavities the lung on that side becomes completely airless pasty blue in color and is plastered against the pericardium or against the vertebral column The pleural exudate at first is serosanguinous then becomes greenish brown and turbid and is filled with streptococci degenerated polymorphonuclear leucocytes and shreds of fibrin Later the fluid becomes more purulent

The inflammatory exudate begins to organize very rapidly in the lung and bronchi in the parenchyma and in the pleura The alveolar and bronchial walls the adventitia of the blood vessels and the interlobar septa all become thickened by the connective tissue proliferation Absorption of the exudate is hampered by the fibrosis of the lymph channels The pleura becomes thick with marked vascularization resulting from the organization of the fibrinous exudate giving rise to firm and permanent adhesions and often pocketing of encapsulated pus

Occasionally multiple areas of necrosis develop in the lung parenchyma with

cases of hematogenous streptococcus pneumonia occurred among 63 patients with hemolytic streptococcus septicemia that were observed during the same period Keefer and associates[40] observed metastatic pneumonia in 7 3 per cent of 246 cases of hemolytic streptococcus bacteremia at the Boston City Hospital, and Schwartzman and Goldman[40b] noted it in 8 of 168 cases of hemolytic streptococcus septicemia at Mount Sinai Hospital New York Netter[6b] suggested that all bronchopneumonias are caused by agents which come from the mouth and are, therefore superinfections occurring after other contagious diseases The hemolytic streptococcus itself, while frequently associated with pharyngitis tonsillitis and sinusitis, seldom is invasive enough under these circumstances to produce pneumonia During the course of certain infections notably measles and influenza there appears to be a local loss of resistance which permits the streptococcus to penetrate and to spread to the trachea and bronchi The rich lymphatic supply in this region permits the organisms to spread to the regional lymph nodes and the interstitial tissue of the lungs Reimann[1] suggested that the tendency of this type of infection to spread may be due in part to the ability of the hemolytic streptococcus to delay the coagulation of plasma or exudate and to dissolve fibrin

Pathology

Descriptions of the pathology of streptococcus pneumonia have been given by Finkler[1] Ribbert , Mathers[9] MacCallum [11], Glomset[11], Cole[13] and Menten and associates[19] Many of the descriptions are from cases which occurred as complications of measles and influenza in the United States Army Camps and have been collected by Callender[11]

The inflammatory reaction involves the larynx, trachea and entire bronchial tree as well as the lung The mucous membrane of the larynx, trachea and bronchi exhibits a characteristic dark red color which may be due to the laking of blood There is usually intense hyperemia and even hemorrhage in these structures and there may be actual necrosis of the thyroid cartilage, arytenoids and bronchial walls and occasionally destruction of the epiglottis and vocal cords The severest reactions have been observed in very acute cases especially in those complicating measles

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be either high or low continuous or remittent With the accumulation of fluid the pleuritic pain usually disappears but dyspnea increases and may become extreme The cough may be very irritating Early, the sputum may be muco purulent but this soon becomes rusty or blood streaked and sometimes grossly bloody Vomiting may occur particularly in infants and children

Physical Signs

The general appearance of the patient is one of severe toxicity with increasing respiratory distress The throat may be diffusely injected but often the pharyngeal vessel are engorged and the fauces injected and sometimes there are petechial lesions on the soft palate and the papillae of the tongue may be enlarged almost as in scarlet fever Prostration appears early and progresses to a typhoid like state The dyspnea increases rapidly and the color of the lips and sometimes of the ears and cheeks becomes cherry red and later assumes a violaceous or even an ashen hue

Herpes of the lips may occur but it is unusual In some instances a scarlatiniform eruption appears or the skin may be pigmented and there may be some petechiae in the axillae and groins as in scarlet fever The pulse is rapid and increases progressively with the dyspnea that accompanies the accumulation of fluid in the chest

In the lungs the signs are quite variable There may be definite signs of localized areas of consolidation but these rarely are extensive enough to suggest complete consolidation of the lobar type Even when extensive consolidation is made out however there are almost always musical and fine crepitant rales over a limited area in one lobe while other areas show atypical consolidation involving an entire lobe or lobes

The outstanding feature in very many patients is the rapid accumulation of fluid in the pleural cavity which is accompanied by typical physical signs This can be easily surmised from the rapid increase in the patient s dyspnea cyanosis pulse rate and toxemia

Laboratory Findings

The total white blood cell count usually is elevated to about 20 000 per cu mm but may rise as high as 40 000 or more The increase is mostly in mature and immature polymorphonuclear leucocytes and these may contain numerous toxic granules The leucocytosis usually persists until the fluid in the chest is drained In occasional cases there may be a leucopenia The latter is encountered most frequently in the cases which occur following epidemic influenza Anemia of moderate and sometimes severe degree may develop in the course of the disease

the formation of abscesses containing numerous streptococci which are discharged usually through the bronchi Occasionally these abscesses rupture into the pleura giving rise to a pyopneumothorax or a bronchopleural fistula The infection usually remains fairly localized due to the rapid fibrosis in the respiratory tract Septicemia, therefore, is not common except perhaps as a terminal event Other organs are hardly affected in the interstitial form

In the second type, which MacCallum[5] arbitrarily designated as lobular pneumonia the streptococci apparently invade in the same manner, but there is much less tendency to walling off In this form the cut surface of the lung often exudes thin, red pus Instead of the the firm peribronchial nodules there are patches of consolidation in which the alveoli are filled with blood and leucocytes and contain enormous numbers of streptococci Much of the blood is laked and the red blood cells appear on microscopic examination as shadows which often coalesce into a network of pink staining hyalin material There are no interstitial changes and there is no tendency to walling off by fibrosis Instead there is widespread necrosis with eventual destruction of large areas of lung tissue usually accompanied by hemorrhage Subpleural hemorrhages and areas of necrosis are seen readily There is often a pleural effusion, but there is no tendency of the exudate to show organization

This form may be pure or it may be found along with the interstitial type It was observed frequently in the more rapid and fatal form of streptococcus pneumonia which occurred during the influenza epidemic of 1918 In this form there may be changes also in other organs Mathers[9] noted parenchymatous degeneration of the kidneys liver and myocardium and also petechial hemorrhages in the gastrointestinal tract and in the kidney pelvis Pericarditis and occasionally mediastinitis may occur

Symptoms

The onset of streptococcus pneumonia usually is gradual and occurs during the latter part of or within a few days after the antecedent infection Sore throat is very frequent during these antecedent infections This together with hoarseness which results from the laryngitis that so frequently is an early manifestation, serves to differentiate the disease from a primary pneumococcus infection The earliest symptoms are increasing malaise fever cough and prostration Less often the onset is sudden and begins with a chill This occurs in 10 per cent or less of the cases Occasionally the first symptom may be pleuritic pain but this is neither as frequent, as severe nor as persistent as that which occurs in lobar pneumonia, and it is more common to have presternal distress or pain either alone or in association with the pleuritic pain The fever varies the temperature may

Complications

As already noted, the most common complication of hemolytic streptococcus pneumonia is empyema. This occurs early and while the pneumonia is still progressing. The incidence varies, but it usually occurs in 60 per cent or more of the cases (Cole[1], Sharp, and Trask[17]). In Lawrence and Sutliff's cases, only 3.2 per cent had empyema. This complication was present in all of the fatal cases of measles bronchopneumonia in Clendening's series.[1] It has been found less frequently among the colored (20 per cent) than among the white troops (40 per cent) at Camp Dodge. Abscesses in the lung are common. These are usually small and heal by draining through the bronchi. Occasionally they rupture into the pleural cavity and give rise to pyothorax. Less often they become reinfected with other organisms and give rise to chronic lung abscess. Pericarditis is also a relatively frequent occurrence, particularly among the severe cases with empyema. Mediastinitis, endocarditis and peritonitis occur also but are less frequent. Remote metastatic infections such as phlegmon and arthritis may occur. Residual bronchitis, bronchiectasis, lung abscess, emphysema and pulmonary fibrosis may persist as late complications resulting from the early intense inflammatory reactions, necrosis and subsequent fibrous tissue replacement. In addition there may be transient auricular fibrillation during the acute illness, particularly during periods of severe respiratory distress. There may also be toxic psychoses. Thrombophlebitis may occur during the latter part of the acute disease or during convalescence.

Diagnosis

The signs and symptoms of hemolytic streptococcus pneumonia usually are so characteristic that the diagnosis often can be suspected clinically. It should be considered when signs of acute pulmonary infection are made out after a patient has had a sore throat or laryngitis and in the pneumonias which follow influenza and measles. The early appearance of fluid in the pleural cavity during the acute phase of the pneumonia strongly suggests a streptococcus etiology. The diagnosis also is strongly to be suspected with the finding of streptococci in large numbers as the predominant organism of the sputum. The diagnosis is established if a pure culture of hemolytic streptococci is obtained from lung suction or from the first fluid obtained by thoracentesis or in a blood culture in a patient in whom the first symptoms are those of an acute febrile illness suggesting a pulmonary infection. In making smears of pleural fluid it should be borne in mind that streptococci sometimes may appear as diplococci, but they can be differentiated readily from pneumococci by culture on blood agar plates. In smears of

This is usually of the normocytic variety There is often rouleaux formation which may give rise to difficulties in the typing of blood for transfusion, but this may be overcome by diluting the blood with equal parts of saline It is due probably to an increase in the fibrin content of the plasma and also to an increase in other serum globulins

The sputum may be green and mucopurulent in character, or it may be blood streaked or grossly bloody Smears show many leucocytes and characteristic chains of streptococci When cultured on the surface of blood agar plates, the typical beta hemolytic streptococci are found in large numbers

Positive blood cultures are relatively infrequent There were 7 bacteremic cases among 55 in Keefer s series and only 1 of his 16 cases of empyema was bacteremic Trask obtained positive blood cultures of hemolytic streptococcus in 6 of the cases in which the cultures were made during life, and in 8 of 15 patients in whom cultures were made on the heart s blood at autopsy The blood cultures may be negative throughout the course and then become positive only in the last days of life in the fatal cases

The empyema fluid obtained by thoracentesis usually is serosanguinous and contains fine strands or flecks of fibrin Smears made of this exudate show degenerated polymorphonuclear leucocytes and many streptococci Hemolytic streptococci are grown from such fluids in pure culture Only rarely are sterile fluids obtained from the pleural cavity except after sulfonamide therapy

Course of the Disease

In the favorable cases the termination is with a slow drop in fever and pulse rate This may occur quite rapidly and in a very striking manner immediately after a large accumulation of fluid has been removed from the chest The toxemia and dyspnea improve rapidly The subsequent course then depends upon the amount and fate of the accumulation of fluid in the chest and the extent of destruction of lung tissue

In the less favorable cases toxemia dyspnea and cyanosis increase to a point where the patient manifests exhaustion The signs then are those of circulatory collapse with sweating and ashen gray color rapid thready pulse and low blood pressure Frequent removal of fluid from the pleural cavity may serve to tide the patient over the severe acute stage of the infection in the lung until the fluid becomes more purulent and can then be dealt with surgically Death in cases of hemolytic streptococcic pneumonia may occur early as a result of the toxemia and the extensive involvement of the lung and pleura or it may occur later because of multiple foci of infection or the patient may die after drainage of the pleural cavity has been instituted

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sputum streptococci may occur in many other conditions, but hemolytic streptococcus pneumonia should be considered if large numbers of these organisms are obtained from a good specimen of sputum raised from the bronchi Serological and immunological tests are of no great help In the differential diagnosis one must consider other forms of pneumonia such as those due to pneumococcus staphylococcus influenza bacillus and Friedlander's bacillus The diagnosis is established by the cultural identification of the bacteria

Locke [9] in correlating the bacteriology of sputum and pleural fluid found that the most common error observed in his cases was to find a pneumococcus usually of group IV in the sputum and pure cultures of hemolytic streptococci in the pleural fluid This occurred 21 times in 478 cases This error probably was due in part to the method of sputum examination which was designed primarily for isolating and identifying pneumococci Mouse inoculation was relied on to a great extent for this purpose and this method may fail to yield streptococci, particularly when mouse virulent pneumococci are present also in the pharynx The possibility of hemolytic streptococcus reinfections in pneumococcus pneumonia may contribute also to this lack of correlation The frequent association of streptococcus pneumonia with tuberculosis also must be borne in mind Often tuberculosis is not recognized or diagnosed until well along in convalescence Possibly the streptococcus pneumonia serves to activate latent tuberculosis but it also occurs in patients in whom there is known to be an active tuberculous lesion

PROGNOSIS

The mortality from streptococcus pneumonia as pointed out by Keefer[3] and by Reimann[1] depends on a number of factors which include age bacteremia the extent of the lung involvement the complications and the severity of the antecedent illness or of the associated debilitating diseases While there are considerable variations in the death rates reported from different sources they tend generally to be high In Bullowa s series[14] the fatality rate for 177 cases of all ages was 33 per cent It was 30 per cent in those under 2 years of age, 17 per cent in older children and 41 per cent in adults In bacteremic cases of all ages the mortality was 89 per cent In Cole s cases[15] there were 43 per cent deaths, and Cecil and Lawrence[4] reported a mortality of 47 per cent among private patients most of whom were hospitalized The mortality in Lawrence and Sutliff s cases[16] was 12 3 per cent in those in which only the hemolytic streptococcus was obtained and 6 per cent in the cases where the sputum yielded both pneumococci and hemolytic streptococci Among infants and children Trask[17] reported a mortality rate of 63 per cent

During epidemics the mortality may be high even among young adults For example there were 48 per cent deaths among patients with hemolytic strepto coccus bronchopneumonia complicating measles at Fort Sam Houston [4] At Camp Dodge[10] it was noted that the mortality from uncomplicated hemolytic streptococcus pneumonia was higher among colored troops 20 per cent than among whites 11 per cent On the other hand when empyema developed the mortality among the colored troops was lower 44 per cent than among the whites 65 per cent

The figures that have been quoted were obtained mostly before the wide spread use of sulfonamide therapy, and only small numbers of cases have been reported recently Since however no considerable epidemic of hemolytic strep tococcus pneumonias has been recorded in which sulfonamide therapy was used it is not possible to tell how much of a reduction in mortality can be expected from this form of treatment

John[13] found a high leucocyte count to indicate a favorable prognosis This however, is not always true since severe cases with massive empyema which so often are fatal may have extremely high white blood cell counts Among cases of streptococcus empyema at the Boston City Hospital the mortality was 45 per cent [1] In Locke s earlier series of cases of empyema from the same hospital all of 12 unoperated cases died and there were 24 per cent deaths among those in whom surgical drainage was used[2] In the hemolytic streptococcus empyemas of children Lanman and Heyl reported a mortality of 33 per cent while Powers [4] reported 57 per cent deaths in the cases observed at the New Haven Hospital from 1927 to 1937 and no deaths in 12 consecutive cases treated with sulfonamide drugs from 1937 to 1940

Prophylaxis

According to Blake[4] it is not the chronic carriers who are responsible for the spread of hemolytic streptococci but rather the acute carriers that is patients who are actually ill or convalescing from hemolytic streptococcus infections It is for that reason that emphasis has been placed on isolation of cases and the prevention of the spread by droplet infection During World War I Capps devised an elaborate system for prevention of droplet infection by the use of masks and improvised cubicles in the form of sheets hung between the cots and across the tables in the mess halls The extent to which the infection is prevented in this manner is difficult to evaluate Recent studies have centered about the use of methods to sterilize the air by means of ultraviolet irradiation and by sprays of germicidal aerosols In addition attempts to eliminate streptococci from cases and carriers by the use of sulfonamide drugs or with bacteriostatic enzymes such

as tyrothrycin or penicillin are being made. The results of any or all of these measures are difficult to evaluate at the present time. The strictest isolation of patients with severe upper respiratory infections, particularly measles and influenza, is most essential when hemolytic streptococci are known to be prevalent.

Treatment

The supportive and symptomatic treatment of hemolytic streptococcus pneumonia is essentially the same as for cases of any other severe pneumonia. Because of the intense dyspnea and cyanosis, oxygen is required frequently and must be used in high concentrations. When the toxicity, cyanosis and dyspnea are the result of the accumulation of a large amount of fluid with displacement of the mediastinum, it is essential to resort to the removal of the fluid by thoracentesis. This procedure usually brings about a most dramatic improvement which, however, often is only temporary.

As in most of the acute bacterial infections the chief reliance is now placed on the use of sulfonamide drugs. Keefer and associates[7] have noted that the response of hemolytic streptococcus pneumonia to sulfanilamide and sulfapyridine is not nearly so dramatic as in pneumococcus pneumonia. In their cases the incidence of empyema was not reduced, and the course of the disease was not materially shortened, but the mortality probably was lowered. Since their report the results in the small number of cases treated with sulfadiazine at the Boston City Hospital have been more encouraging.[4] Sulfadiazine appears to be more effective against the hemolytic streptococcus than sulfanilamide and sulfapyridine, both from studies in vitro and in experimental animals as well as from clinical experience. It is also considerably less toxic. In particular the use of sulfadiazine in these cases is advantageous because it is not accompanied by the cyanosis and the progressive anemia which so regularly result from sulfanilamide administration.

In the treatment of the hemolytic streptococcus pneumonias with sulfonamide drugs it is important to maintain high blood concentrations and to continue treatment much longer than in cases of pneumococcus pneumonias. Doses adjusted so as to maintain blood concentrations of free sulfadiazine between 10 and 15 mgm. per 100 c.c. or even higher are desirable during the acute febrile stage; somewhat lower doses should be used after the temperature has been normal for a few days. Because of the tendency for abscess formation and the pocketing of fluid in pleural spaces it is desirable to maintain the treatment for 7 to 10 days, and sometimes even longer, after the temperature has reached normal. During the acute febrile stage it may be necessary to resort to doses of 8 or 9 gm. per day in the average adult. It is often desirable to give the usual dosage of

1 gm every 4 hours by mouth and to supplement the oral doses with an additional 2 or 3 gm of sodium sulfadiazine administered parenterally at irregular intervals whenever it is found that adequate levels are not being maintained. The sodium sulfadiazine may be given intravenously as a 5 per cent solution in distilled water or it may be given as a ½ or 1 per cent solution in physiological saline either subcutaneously or intravenously.

One of the most important lessons gained from the costly experience in the epidemics that occurred in the army camps in World War I was the danger of early surgical intervention in acute streptococcus empyema while the pulmonary lesion is still progressing. The fatality rate under these conditions was very high and deaths occurred very soon after the open drainage. When early and repeated aspirations of fluid were resorted to there was a marked reduction in this mortality. It was necessary to follow these procedures later by closed catheter drainage and if this proved to be inadequate rib resection was carried out after the fluid had become thick and well walled off.

The surgical methods are still necessary even in cases treated with sulfonamide drugs. With the chemotherapy however a larger percentage of cases now recover from the empyema and many clear up with aspirations alone. Of the 12 cases of hemolytic streptococcus empyema treated by Powers with sulfanilamide or sulfapyridine none died and 7 recovered without resort to thoracotomy. At the Boston City Hospital there have been a number of complete recoveries from hemolytic streptococcus pneumonia in which the only treatment was sulfadiazine. Some of these patients had positive blood cultures and others had infected pleural fluids which resorbed completely after one or more thoracenteses. Intrapleural injection of the sulfonamide drugs does not seem necessary although reports of cases treated adequately by this method are not available nor is the extent of the absorption of these chemicals from the pleural cavity known.

Powers has observed that continuous treatment with sulfanilamide and tapping of the chest may in some children result in a chronic empyema with a very thick fibrin wall. The empyema then fails to drain properly until it is treated surgically and even then the healing is very slow. It is possible that this marked deposition of fibrin in such cases is the result of inhibition of the fibrinolytic action of hemolytic streptococcus when subject to the bacteriostatic action of sulfonamides. The failure of empyema to heal has been noted in some instances in spite of apparent sterilization of the fluid.[2] Where the fluid remains infected and fails to respond to treatment it is possible that bacteriostatic enzymes like penicillin may effect a rapid sterilization and perhaps absorption and healing.

A large variety of antistreptococcus sera and antitoxins have been used with varying degrees of success (Amoss and Craven[3] Dufourt and Sedallian

Manoussakis[4]) Polyvalent antistreptococcus sera and scarlet fever or erysipelas antitoxins have been employed, and these have been administered intravenously and intramuscularly in large doses Amoss and Craven[36] have succeeded in eliminating hemolytic streptococci from the empyema by direct injection of such sera into the pleural cavity but this procedure failed to produce improvement in their cases because of the presence of other organisms This form of therapy has not gained wide acceptance and has hardly been used since the introduction of the sulfonamides It may still be useful in some highly toxic cases and particularly those associated with a scarlatiniform rash In view of Trask and Blake s observation it is best to use a polyvalent antitoxin Immunotransfusions have been suggested (Lyons[4]) for other hemolytic streptococcus infections and may be useful in individual cases The identification of immune donors however is a highly specialized and laborious procedure which most laboratories are not prepared to carry out

Because of the prolonged course of the cases particularly those with empyema, the maintenance of nutrition is essential The diet should be of high caloric value and also high in vitamin content or additional vitamins should be given Small repeated transfusions are useful to combat the progressive anemia which is characteristic of the course

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CHAPTER XXVIII-B

STAPHYLOCOCCUS AUREUS PNEUMONIA

By MAXWELL FINLAND

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While the staphylococcus is a highly prevalent organism in the human environment, virulent strains of staphylococcus aureus are not found with great frequency and in abundance in the normal human respiratory tract. When it occurs there in large numbers, particularly following severe respiratory infections like influenza, it may give rise to a severe pneumonia. When staphylococcus pneumonia occurs after simple infections of the upper respiratory tract, it may be considered primary. Metastatic infections of the lung also occur as part of the general picture of staphylococcus septicemia or pyemia.

HISTORICAL REVIEW

The association of the staphylococcus with certain cases of bronchopneumonia has been recognized since the influenza pandemic of 1889. At that time and

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HISTORICAL REVIEW

The association of the staphylococcus with certain cases of bronchopneumonia has been recognized since the influenza pandemic of 1889 At that time and

almost all of these cases was based on cultures made directly from the lung In Cole's[17] series of 211 cases of primary atypical pneumonia in adults which we e included by Reimann 9 per cent were considered to be staphylococcus aureus pneumonias In these cases the etiological diagnosis was based on the predominant organism found in the sputum or on it being the only organism found in the blood culture during life or from the lungs at autopsy In Bullowa's[1] series of 6 1 8 cases of lobar and bronchopneumonia which included all age groups the incidence of staphylococcus pneumonia was 1 1 per cent in the entire series 2 0 per cent in the fatal cases, 2 1 per cent among children and 0 6 per cent in adults The incidence in children under 2 years was the same as in older one Trask also found an incidence of 2 2 per cent among his 553 cases of pneumonia in children In a nation wide survey of the etiology of pneumonia made by Rumreich and associates the staphylococcus was listed as the etiological agent in 1 19 per cent of 25 802 cases of pneumonia of all kinds in 0 82 per cent of the cases of lobar pneumonia and in 2 0 per cent of the ca es of bronchopneumonia These discrepancies may be explained in part by the fact that more complete bacteriological studies were made in those cases in which the incidence was high while in tho e with a low incidence the focus of attention was chiefly on the isolation and identification of pneumococci

According to Cohen and Neuhoff and Berck [1] the staphylococcus is the most common cause of empyema in infants and the former believes that the incidence of staphylococcus pneumonia in children is increasing That has been true also both in children and in adults at the Boston City Hospital The prevalence of staphylococcus pneumonia in circumscribed outbreaks during epidemics of influenza has been mentioned already During the 1940–41 epidemic of influenza in Boston it was shown that the staphylococcus infection in the lungs of different individuals assumed a large variety of forms varying from simple tracheobronchitis with minimal pulmonary involvement to a fulminating acute and fatal hemorrhagic and edematous pneumonia or a chronic organizing pneumonia with bronchiectasis and multiple lung absces es In addition a number of cases of pneumococcus lobar pneumonia occurring during the same period howed re infection of the lung with staphylococcus The marked increase in the incidence of staphylococcus pneumonias including both primary and secondary cases continued for some time after the influenza epidemic subsided

The primary staphylococcus pneumonia is more common in the winter and spring The secondary or metastatic staphylococcus infections on the other hand may occur at all times of the year[11] Outbreaks of staphylococcus pneumonia have occurred al o in neonatal wards where the pulmonary infections spread along with other pyogenic staphylococcus infections among the infants the mothers and the nursing staff [23]

even earlier a number of writers noted necrosis of bronchi and of the alveolar structure of the lung in cases of influenza and staphylococci were obtained in cultures of some of these cases (Leichtenstern[1]) Netter in a study of the bacteriology of bronchopneumonia found staphylococci in 3 out of 39 cases in adults from which a single organism was obtained in pure culture and in 8 of 14 additional cases with mixed infections Two of those having pure cultures of staphylococci had multiple small abscesses, and the other had " splenization " of the lung In infants and children he found staphylococci in 5 out of 25 cases with pure cultures and in 8 of 17 having multiple organisms Fraenkel[3] described a case of bronchopneumonia in which the sputum was first thin and pink in color and later became abundant and purulent Repeated aspirations of material directly from deep in the lung yielded thick gray green pus from which pure cultures of staphylococci were obtained Later there were definite physical signs of cavitation in the same region

During the influenza pandemic of 1918 there were several reports indicating that the staphylococcus played a dominant role in the severe complicating pneumonias in certain regions The most extensive outbreak of this sort was described by Chickering and Park[4] and occurred at Camp Jackson South Carolina Among 1 409 patients with pulmonary complications of influenza that occurred at this camp there were 385 deaths Cultures made of the lungs of 312 of the fatal cases yielded a staphylococcus as the only or predominant organism in 153 cases Two similar but less extensive outbreaks were reported in other military hospitals during the epidemic (Tytler and associates Patrick[6]) Since that time other groups of cases have been reported Some were sporadic cases, and others occurred in association with influenza (Burgess and Gormley[7], Reimann[8] Macgregor[9] Cohen Kanof and associates[11] Gaspar[12] Baker[13] Michael[14] Finland and associates) During a recent outbreak of influenza that occurred in Boston the staphylococcus again attained epidemic prevalence in the complicating pulmonary infections[11]

Occurrence and Epidemiology

The exact incidence of staphylococcus pneumonia is just as difficult to determine as the incidence of hemolytic streptococcus pneumonia and for the same reasons that were outlined in connection with the latter (see Chapt XVIII-A just preceding this chapter) It is not surprising that there are wide variations in the frequency with which the staphylococcus has been found as a cause of pneumonia by different observers Staphylococcus pneumonia comprised approximately 10 per cent of the 700 cases of primary atypical pneumonia collected from the world literature by Reimann The bacteriological diagnosis in

come invasive locally or they are aspirated and establish themselves first lower down in the larynx trachea or bronchi McCordock and Muckenfuss[27] demonstrated an enhancement in the local virulence of staphylococci in rabbits by vaccine virus When these workers used both staphylococci and vaccine virus they were able to produce bronchial and pulmonary lesions in rabbits but each of these agents separately failed to do so In humans also it may be presumed that the viruses of the simple upper respiratory tract infections act in a similar manner to enhance the pathogenicity of the staphylococcus

In young infants particularly in premature ones who have difficulty in nursing aspiration of infected material plays an important role (Johnson and Meyer Gasul and Singer Glaser and Landau[0] Macgregor Gaspar[1]) The presence of aspirated material sometimes can be seen in microscopic sections of the lungs of infants with staphylococcus pneumonia

In occasional cases there is a history of some pyogenic infection of the skin several days or weeks preceding the onset of a staphylococcus pneumonia which otherwise appears to be primary and bronchogenic This would suggest a possible hematogenous source similar to that found in cases of known metastatic infections in patients with staphylococcus aureus pyemia and septicemia arising from a known active focus Unlike the latter cases however the original focu in the primary cases usually is healed and there is usually also an antecedent influenza or other upper respiratory infection In these respects the bronchogenic cases differ from those which are truly metastatic in origin It is therefore more likely that the furuncles or abscesses found earlier in the apparently primary cases are only evidence of the presence of staphylococci in the host The organisms presumably are present also in the upper respiratory tract and the lung infection is thus of an autogenous source Thus Macgregor[9] was unable to demonstrate septic thromboses in the pulmonary arteries of a case in which there had been a septic infection of the umbilicus

PATHOLOGY

Numerous descriptions of the pathology of staphylococcus pneumonia are available (Chickering and Park[4] Tytler and associates Reimann Macgregor[9] Kanof and associates[1] Gaspar[1] Baker[13] Wollenman and Finland[1]) All agree in most of the essential details There are two main varieties of pathological pictures and these correspond to the clinical course One is the acute hemorrhagic type which is seen most frequently during influenza epidemics The other is the subacute or chronic type in which the results of tissue destruction and fibrosis are a prominent feature

In the acute staphylococcus pneumonias the lungs are increased in size and

Etiology

In almost all instances the staphylococcus has been identified as *Staphylococcus aureus* and there is some doubt as to whether *Staphylococcus albus* can cause definite lesions in the lung. The strains recovered from the lungs or from sputum usually are strongly hemolytic and they vary considerably in their production of alpha and beta toxins. The production of a powerful erythrotoxin by some of these strains may account for the occurrence of scarlatiniform eruptions in occasional cases of staphylococcus pneumonia. All of the strains that have been studied have been classified, on the basis of their cultural and biological characteristics as *Staphylococcus aureus* of the human virulent variety, give a positive coagulase reaction and fall into the type A of Julianelle[15].

Predisposing Factors

There is usually an antecedent history of coryza or some other mild respiratory symptoms. Influenza in epidemic form is by far the most important predisposing factor. In Reimann's cases[8] the primary bronchogenic pneumonias were superimposed on other conditions which presumably depressed the defense mechanism. These included asthma, bronchitis, clinical influenza, sore throat, chronic nephritis and malnutrition. Cohen[3] considered the disease to be most frequently primary and Kanof and associates[11] also found no special predisposing factors except that in occasional cases there had been a long debilitating illness. In 10 of the latter's 25 cases there was a simple upper respiratory infection of 1 or 2 days duration and 80 per cent of them had an acute pharyngitis. They felt that most of their cases had some antecedent virus infection. Influenza A virus indeed has been isolated in individual cases of staphylococcus pneumonia occurring during epidemics (Stokes and Wolman[4], Stuart Harris and associates[5]), and the development of antibodies against this virus in the course of the staphylococcus pneumonias has been noted (Stuart Harris and associates[5], Michael[14], Finland and associates[1]). Of the 12 cases reported by Trask[10] 10 had a cold or influenza, 1 had measles and 2 of the cases were hospital infections.

Pathogenesis

There is good evidence for the bronchogenic origin of the lung involvement in cases of staphylococcus pneumonia. In some patients the disease begins as a membranous laryngitis and bronchitis[15, 6]. It may be presumed that during the antecedent upper respiratory tract infection which occurs in most instances, the organisms in the throat and sinuses have an opportunity to multiply and to be

In the more fulminating cases the involved lobes are heavy and moist and they exude an abundance of bloody fluid Microscopically the picture in such lobes is predominantly one of hemorrhage and edema with very little fibrin and only a few polymorphonuclear leucocytes Nevertheless many groups of cocci can be seen In spite of the meager leucocyte response there is a necrosis of the walls of the alveoli and often many of them contain suggestive hyaline membranes The bronchi in such cases show marked edema and necrosis with very little cellular reaction In uninvolved areas the alveoli are distended and some are disrupted and form emphysematous blebs Cultures from the lungs in all such cases yield an abundant growth of staphylococcus aureus usually in pure culture Cultures of the blood at autopsy most often are sterile Occasionally other organisms especially hemolytic streptococci are found in the lungs

In subacute and chronic cases the outstanding features are the abscess formation and the extensive fibrosis and organization Grossly the lungs vary in size but usually are not markedly enlarged and they appear quite distorted There are extensive pleural adhesions but there are no areas with fresh exudate or fibrin The pleural surfaces of the lungs present a mottled appearance which varies from dark grey red in the posterior portions to grey pink in the areas of emphysema The latter are most prominent in anterior portions of the upper lobes and in the periphery of the lungs The basal portions usually contain firm rubbery nodular areas especially posteriorly In some cases the major involvement may be limited to one lobe or one lung

On section the nodular areas are seen to consist of large cavities with firm well demarcated walls the majority containing yellow and grey green mucoid exudate which can be expressed from the cavities Most of the cavities communicate with bronchi which in turn are plugged with similar exudate There is extensive fibrosis between the cavities where the usual architecture may be replaced almost completely by fibrous tissue In other areas the tissue appears either emphysematous or firm and dull red grey in color The cut surface is moderately dry The trachea bronchi and bronchioles contain grey green tenacious exudate which when removed reveals an apparently intact but red mucosa The blood vessels show no marked change

Microscopically there is evidence of extensive fibrous replacement of alveoli Large abscesses are in communication with bronchi forming bronchiectatic cavities The bronchial walls are infiltrated with numerous plasma cells scattered lymphocytes and histiocytes and rare foreign body giant cells The abscess cavities are filled with a more acute inflammatory exudate and their walls show some persistence of a necrotizing process In some cases particularly in young infants and in some old persons aspirated material can be seen The alveoli in the areas of interstitial fibrosis are lined by low cuboidal epithelium and there

weight There is usually no definite exudate over the pleural surfaces, although a moderate amount of thin fluid may be present in the pleural cavity Such fluid usually yields *Staphylococcus aureus* on culture The lungs completely fill the pleural cavity and maintain their shape when they are removed from the thorax Externally they present mottled grey to dark red purple anterior surfaces which blend into plum colored and mottled posterior surfaces There may be areas in the lung suggesting infarcts Scattered throughout the posterior and inferior portions there are nodular areas which on the cut surface present a homogenous dirty grey appearance and exude mucoid exudate When this exudate is scraped away, multiple abscess cavities are revealed which vary from 1 to 5 mm in diameter many coalescing to form honeycombed cavities 1 to 2 cm in diameter These abscesses in general are arranged in relation to bronchi and bronchioles and usually communicate with them There is no evidence of a well defined wall to these abscesses and the contiguous parenchyma appears markedly necrotic fading into apparently intact alveoli filled with exudate The intervening lung presents a varied appearance In some areas it is extremely wet, subcrepitant and exudes frothy bloody fluid while in others the grey exudate filled alveoli can be distinguished Most of the lung is involved, and only a small part remains air containing The trachea and bronchi are filled with plugs of yellow grey tenacious exudate In some cases there is an ulcerative and diphtheritic type of laryngo tracheobronchitis The pulmonary arteries and veins appear grossly normal In occasional cases there is evidence of an acute pericarditis with thin yellow turbid fluid

In the microscopic sections there is seen an extensive destruction of the usual architecture by an acute necrotizing process This is most marked about the bronchi the bronchioles and the adjacent alveolar tissue The bronchi and bronchioles are almost completely denuded of their mucosa and their walls infiltrated with acute inflammatory cells chiefly polymorphonuclear leucocytes and histiocytes and an abundance of fibrin In some of the acute cases there is a hyaline alveolar membrane similar to that which is prominent in all kinds of acute influenzal pneumonia There is necrosis of the alveolar septa beyond the bronchioles resulting in the formation of abscesses which vary in size from small miliary abscesses to large conglomerate necrotic masses having no limiting wall of connective tissue nor any evidence of organization of the exudate In some sections large veins can be seen projecting into the abscess These veins are infiltrated with inflammatory cells and some of them contain fibrin thrombi in their lumens Elsewhere the blood vessels are ruptured, and the alveoli are filled with blood In other areas the alveoli are filled with edema fluid but contain no blood Large numbers of cocci are seen in groups and clusters scattered about in the exudate both in the alveoli and in the lumens of the bronchi

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PHYSICAL SIGNS

The appearance of the patient is one of marked sepsis and progressive respiratory embarrassment There is an anxious facial expression and a deep cherry red cyanosis of the lips Herpes is seen rarely The patient is obviously dyspneic and sometimes shows inspiratory and expiratory stridor from laryngeal obstruction

In the later stages of the severe cases the skin is moist and clammy In rare instances scarlatiniform eruptions which are indistinguishable from those of scarlet fever have been noted

The temperature usually is high and may reach levels of 104 to 106 F with occasional remissions to 100° or 101 F In some instances the fever is of the septic type The pulse is relatively slow particularly in the cases which follow influenza In Chickering and Park s series the pulse rate rarely rose above 100 and it was over 120 only late in a few of the fatal cases The respirations are rapid from the start and usually are between 40 and 60 per minute There is early abdominal distention which is almost as severe as in patients who have extensive peritonitis

The signs in the lungs are very atypical Early they may be absent or there may be only a few musical or crepitant rales In some instances in addition there may be some diminished resonance and no other signs throughout the course In most instances however showers of consonating rales appear and signs of scattered areas of consolidation are made out but rarely are these extensive enough to suggest involvement of an entire lobe and then only late in the disease Usually the signs are diffuse and all lobes are involved to some extent Complete consolidation of one or more lobes does occur at times and such cases may have a better prognosis In the cases reported by Kanof and associates [1] 7 out of 8 of those who recovered had lobar consolidation A pleural friction rub may be heard early in the illness and this may be transient or recurrent and may be followed by signs of fluid In occasional cases a pleuro pericardial friction rub is heard

In infants there is usually congestion in the throat and a mucopurulent discharge in the nose with crusting There are rapid grunting respirations and often there is meningismus The signs in the lungs frequently are difficult to make out until the disease is well established

In the prolonged cases dyspnea and cyanosis are prominent throughout and are difficult to influence by oxygen The signs are those of diffuse bronchitis and scattered consolidation with evidence of multiple cavitation When these are prominent in the upper lobes the signs resemble closely those of pulmonary tuberculosis As the disease progresses, there is increasing distention of the cervical veins and engorgement of the liver

is evidence of regeneration of the bronchial mucosa The alveoli contain exudate in different stages of organization Large sheets of young connective tissue can be seen extending from one alveolus to another The arteries in the areas of fibrosis show early proliferative endarteritis

The cultures made at autopsy show staphylococcus aureus as the predominant organism recovered from the lung Occasionally alpha or beta hemolytic streptococci may occur or influenza bacilli can be recovered The heart's blood usually is sterile In occasional cases there is evidence of metastatic infection with abscesses in the myocardium spleen liver and kidneys In some of the more chronic cases in which there is extensive pulmonary fibrosis, there may be hypertrophy of the right ventricle and evidence of congestive cardiac failure

SYMPTOMS

The onset usually is insidious In occasional cases it is ushered in suddenly with a chill with pleural pain or with a high fever cough and rapid respirations There is a rapid increase in the dyspnea Hoarseness is frequent Where laryngitis is marked there may be asthmatic wheezing and even laryngeal stridor, which sometimes is relieved strikingly when the patient after a severe coughing spell raises tenacious fibrinous material that looks like a diphtheritic membrane Occasionally a large cast of the trachea thus may be dislodged Sweating may be present throughout the course There may also be recurrent chills or chilly sensations In those with a fulminating course there is rapidly increasing prostration ending in stupor and progressive dyspnea and air hunger

The sputum in some of the cases of staphylococcus pneumonia is so characteristic that it alone may be diagnostic Typically it is usually described as salmon pink representing a mixture of pus and blood At times there may be gross blood or blood streaking in an otherwise purulent sputum This characteristic sputum may continue for some time but usually it becomes mucopurulent and remains so When the disease occurs in young children or in newborn infants it is preceded usually by a slight cold with nasal obstruction due to mucopurulent exudate Vomiting occurs early and green purulent sputum often can be distinguished in the vomitus Diarrhea and abdominal pain may accompany the vomiting and are associated usually with marked distention Cough begins early and is continuous dyspnea is marked In the fatal chronic type which is encountered mostly in persons over 50 the prominent symptoms are the persistent dyspnea and cyanosis and the patient remains irrational and stuporous throughout the course When staphylococcus pneumonia occurs as a metastatic infection the early symptoms are masked by those of the original septic infection There may be cough and purulent sputum and occasionally pleuritic pain

tuberculosis with cavitation In the favorable cases the large cavities may empty completely and show gradual healing by fibrosis

Course of the Disease

The course of the disease may be fulminating or it may be quite protracted In the former there is a rapid increase in cyanosis and death may occur either from suffocation or from toxemia and circulatory collapse In other cases there is gradually increasing dyspnea with a rise in the pulse rate Death in such cases occurs from increasing anoxemia which usually is accompanied by signs of congestive failure In those who recover signs of cavitation in the lung appear Following this the patient may raise abundant purulent sputum which sometimes contains large amounts of blood and may vary in color from pink to bright red The temperature usually drops by lysis and there is gradual healing In infants and young children there may be a sudden increase in the dyspnea and cyanosis with evidence of marked distress This suggests a rupture of an abscess into the pleural cavity with the development of pyopneumothorax which can be confirmed by x ray or by aspiration While most frequent in infants and young children pyopneumothorax also occurs sometimes in adults

The average duration of the disease in the fatal cases is about 10 days and in those who recover the acute disease lasts an average of about 4 weeks Death may occur as early as 18 hours after the first symptom but the disease usually lasts from 3 to 6 days even in the severe and fulminating cases Chronic cases may have fever and evidence of active infection in the lungs for as long as 2 months or more In such cases there may be transient or terminal septicemia but death usually is due to the increasing pulmonary fibrosis and the resulting cardiac failure Some of the cases seen at the Boston City Hospital died of progressive dyspnea and cyanosis of 8 weeks duration Among those who recover signs of abscesses in the lung or fluid in the pleural cavity may persist and be demonstrable by physical examination or by x ray for as long as 4 months and then clear completely

Complications

The most common complication is empyema the incidence of which varies considerably and may be as high as 75 per cent (Trask [9]) or more In Kanof s cases [1] it was found in 87 per cent of the primary cases and in 58 per cent of those that were secondary It usually begins early as a thin bloody serofibrinous fluid which later becomes thicker until it looks like frank pus Smears and cultures yield a hemolytic staphylococcus aureus in pure culture In occasional cases particularly those treated with sulfonamide drugs sterile effusions may

LABORATORY FINDINGS

The white blood cell count in the very acute cases usually is low, ranging between 6 000 and 14 000 per cu mm In some of the fatal post influenzal cases there may be definite agranulocytosis with a total leucocyte count below 1,000 per cu mm The tendency to leucopenia apparently is a property of the staphylococcus toxin and is observed in the fulminating acute cases in which extreme toxemia and prostration are prominent Schattenberg and Harris[1] succeeded in producing leucopenia in animals with the toxic filtrates of staphylococci In other severe cases both in the fatal ones and in those who recover, the total white blood count may be about normal or it may show a rise to levels of 30 000 or higher The leucocytosis usually is associated with the formation of abscesses in the lung or the development of empyema There is a high percentage of polymorphonuclear leucocytes and young forms in the blood in all cases, even when there is a moderate leucopenia

The sputum as already mentioned is characteristically salmon pink and blood streaked in character Smears show numerous cocci, often in small clusters Direct cultures of sputum yield abundant growth of hemolytic staphylococcus aureus as the only or predominant organism The incidence of positive blood cultures has varied in the experience of different observers Bacteremia may be transient and occur during the early stages or even late in the chronic cases

In the cases reported from the Boston City Hospital bacteremia was demonstrated in 4 of the 21 fatal cases and in 7 of the 41 recovered cases In Bulloway's series 37 per cent had positive blood cultures Most of the strains of staphylococcus obtained from the sputum of patients with staphylococcus pneumonia are mouse avirulent so that the diagnosis obviously would be missed if mouse inoculation were relied on for determining the etiology

The pleural fluid first is thin and serofibrinous in character and later becomes more purulent Smears of the fluid show polymorphonuclear leucocytes and numerous cocci and cultures usually yield abundant growths of hemolytic staphylococcus aureus In Chickering and Park's cases colonies of influenza bacilli were noted also to appear in satellitosis around the staphylococcus colonies on blood agar plates which were permitted to incubate for 72 hours This was not observed in the Boston City Hospital cases during the 1940–41 epidemic

X ray shows diffuse shadows which later become localized In the extensive cases the shadows may be confluent and suggest lobar consolidation Signs of fluid appear early Later cavitation with fluid levels may be discerned These may coalesce to form large abscess cavities with thick capsules When the upper lobe is involved the picture may strongly resemble that of active pulmonary

Kanof and associates[11] have summarized the similarities and differences of staphylococcus aureus pneumonia in children from that due to the pneumococcus The similarities are the seasonal incidence the antecedent upper respiratory tract infection the incidence of bacteremia the same type of temperature curve in many instances the acute onset in some cases the many cases with signs of lobar consolidation the absence of distant foci and the variability of the leucocyte count with the low counts in the patients with a poor prognosis

The staphylococcus pneumonias in children differ from those caused by the pneumococcus in that they predominate in infants less than 1 year old the onset and course more often are fulminating some of those with the insidious onset have a chronic illness empyema is more frequent pyopneumothorax is seen often The empyema fluid differs in that often there is suggestion of bleeding or tissue destruction Diarrhea and abdominal distention are more frequent Renal involvement is more common and the mortality is much higher

Prognosis

The mortality in staphylococcus pneumonia usually is high and has varied in different groups of cases from 30 per cent to over 70 per cent As in the cases of hemolytic streptococcus pneumonia the mortality depends a good deal upon a number of factors which include age the presence of bacteremia and of purulent complications and the severity of the antecedent infections and of the other complicating conditions At the Harlem Hospital (Bullowa) the mortality for all ages was 40 per cent in adults it was 55 per cent and in children 28 per cent Among the latter the death rate was 39 per cent in those under 2 years of age and 17 per cent in those over 2 Of the 19 cases in adults included in Cole s series[17] the mortality was 70 per cent All of Trask s[1] 12 cases of staphylococcus pneumonia in infants and children died Kanof and associates[11] reported a mortality in children of 65 per cent in the primary cases and 83 per cent in those secondary to infection elsewhere In their experience a high sustained fever indicated a poor prognosis and no patient with a low or normal blood leucocyte count recovered

The mortality rates just cited are from cases treated before the introduction of sulfonamide drugs In the cases reported from the Boston City Hospital during the 1940-41 influenza epidemic[13] there were 21 deaths among 62 adults (34 per cent) including 2 deaths in 10 cases of staphylococcus aureus reinfections of pneumococcus lobar pneumonias Most of the deaths occurred in patients over 50 years old or in persons with chronic debilitating diseases Sulfathiazole or sulfadiazine or both were used in most of these cases

The mortality usually is higher in those in which the staphylococcus is re

be demonstrated In some instances the fluid may be pink or red and may even be a dark green or chocolate color Such fluids usually are associated with spontaneous pyopneumothorax

Lung abscesses probably are present in all patients particularly those who survive more than a few days They develop at different rates at least those which are large enough to be demonstrated by physical signs or by x ray These lung abscesses may rupture into the bronchi and heal spontaneously, or they may rupture into the pleural cavity with resulting pyopneumothorax In some instances they may give rise also to a bronchopleural fistula According to Cole[17] and others the abscesses of staphylococcus pneumonia may be the initial stage of many of the chronic lung abscesses that one encounters Pleuritic friction rubs may occur without the development of demonstrable effusions and occasionally there is a pleuro pericardial friction rub Fibrinous and even purulent pericarditis may occur This complication is more frequent in patients who also have empyema

Suppurative otitis media purulent rhinitis sinusitis acute adenitis suppurative parotitis cellulitis and furunculosis may occur in the course of the disease The latter may be associated with a transient septicemia Acute nephritis has been observed especially in children and occasional instances of ureteritis and perinephritis have been noted In acute cases there may be acute cerebral congestion cerebral hemorrhages or a toxic encephalitis Relapses have occurred early in the course of convalescence and sometimes many months after apparent recovery One case has been observed at the Boston City Hospital in which there was a recurrence of a staphylococcus pneumonia with a scarlatiniform eruption and an empyema necessitatis one year after the original pulmonary infection

Diagnosis

The chief features which distinguish staphylococcus pneumonia from other acute pulmonary infections are (1) the characteristic salmon pink sputum which shows a predominance of staphylococcus in smears and cultures (2) the high and remittent type of fever and (3) the evidence of abscess formation in the lung The differential diagnosis from tuberculosis in patients seen for the first time during the subacute or chronic stage when multiple abscesses are present sometimes is difficult The abundant purulent sputum showing staphylococci and the failure to observe tubercle bacilli in the sputum will serve to differentiate the two conditions Sometimes when there is an underlying tuberculosis in the patient with staphylococcus pneumonia particularly when sputum is sparse or absent it may be necessary for a diagnosis to resort to gastric lavage and guinea pig inoculation of the material obtained in this manner

with drug fevers and rashes it may be necessary when such complications arise to change from one of these drugs to the other Recently sulfapyrazine and methyl derivatives of sulfadiazine have been found effective also and it may be possible to resort to them if necessary

Julianelle[5] has used type A antistaphylococcus serum in severe cases with septicemia and staphylococcus antitoxin has been recommended in the severely toxic cases Staphylococcus bacteriophage has been used also (MacNeal and associates[6]) The results of these forms of treatment when used alone or in conjunction with chemotherapy are difficult to evaluate Experimentally there is evidence that the combination of antitoxic serum and sulfonamide drugs may combat the combination of the toxic and invasive factors better than either agent used alone (Farrell) Recent results in experimental animals and in patients have indicated that penicillin may be more effective than sulfathiazole (Powell and Jamieson) but this enzyme has not yet had sufficient clinical trial for a comprehensive evaluation of its effectiveness

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covered from the blood stream during the acute phase In Bullowa s cases there were 23 deaths among 24 bacteremic patients and only 3 deaths among 41 with negative blood cultures In the Boston City Hospital cases 4 of the 11 bacteremic cases died and there were 17 deaths among 51 cases whose blood cultures were sterile The mortality in infants with staphylococcus pneumonia in whom pyopneumothorax develops is extremely high

PROPHYLAXIS

During epidemics of severe influenza if the staphylococcus aureus is known to be prevalent in any given community it may be wise to treat the severe cases of influenza prophylactically with a short course of sulfathiazole or sulfadiazine For this purpose it probably is preferable to use regular therapeutic doses for 2 or 3 days rather than smaller amounts for the same or longer periods

In wards of newborn infants when staphylococcus pulmonary infections are observed it is essential to close the wards to readmissions The nursing staff should be examined carefully for evidence of staphylococcus infections and carriers of pathogenic strains should be excluded Mothers and infants having respiratory infections should be strictly isolated and the infants should be handled with surgical precautions

TREATMENT

The outstanding feature of the general symptomatic treatments that have been used in the past is its striking ineffectiveness Since the introduction of chemotherapy however the results at least in small groups of cases appear to be encouraging Sulfanilamide has had very little observable beneficial effect in cases of staphylococcus pneumonia The results with sulfapyridine were only slightly better although occasional cases seemed to benefit greatly from its use Since the introduction of sulfathiazole and sulfadiazine a number of reports have appeared which indicate that these drugs are quite effective (Beling[31], Melton[14], Michael[14] Finland and associates)

Intensive and prolonged therapy is essential for the best results[15,31] There may be a tendency to relapses if adequate dosage is not maintained It is for this reason that the dosage in cases of staphylococcus pneumonia should not be tapered off after the temperature reaches normal as is sometimes the practice in the treatment of pneumococcus pneumonias Full doses should be continued for 1 to 2 weeks after the fever and symptoms subside and they should be maintained longer if there is evidence of lung abscess or pleural effusion Since the maintenance of sulfonamide therapy for so long a period frequently is associated

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CHAPTER XXIX

ERYSIPELAS

By WILDER TILESTON

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INTRODUCTION

Definition — Erysipelas is an acute febrile disease of the skin or rarely of the adjacent mucous membranes due to the streptococcus and characterized usually by a single area of redness and swelling which is sharply demarcated and extends by continuity

The following description is based on the literature and on a study of 1 7 cases under my care at the Isolation Department of the New Haven Hospital

The best modern publications are those of Roger[18] Lenhartz[16] and Hegler[1] Extensive statistical studies have been made by Anders Sorensen[0] and Pontano[17] Other references will be given in the text

Such an obvious and striking disease could hardly escape notice and good descriptions are to be found in the writings of the ancients though it was often confused with phlegmonous inflammations Its contagiousness was first emphasized by Wells[26] in England in 1800 and was well known to Trousseau[24] The modern history of erysipelas dates from Fehleisen[8] who in 1882 demonstrated

PATHOLOGY

The streptococci are found almost exclusively in the lymphatic vessels of the skin They are most numerous at the margin of the inflamed area and are absent in the central part The exudate consists very largely of serum and small mononuclear cells The internal organs show the usual changes met with in acute infectious diseases viz cloudy swelling and fatty infiltration of the heart liver and kidneys and acute splenic tumor The splenic enlargement is very moderate in extent A terminal bronchopneumonia often is present

CLINICAL DESCRIPTION

The incubation period varies from eight hours to one week with an average of two or three days In experimental erysipelas of man Fehleisen found it to be from fifteen to sixty one hours

The face is involved in about ninety per cent in the remainder the process is in some other part of the skin or very rarely it is confined to the mucous membranes of the upper respiratory tract The lower extremities often are involved the process starting sometimes from a varicose ulcer or from infection of the feet with epidermophytosis (athlete s foot) Erysipelas of the new born usually starts on the trunk either at the umbilical wound or about the genitals

A preceding inflammation of the upper respiratory tract is common and offers a ready explanation of the pathogenesis the streptococcic inflammation may spread directly from the nares or from the auditory canal to the skin or secretion from these parts may be rubbed by the patient into an abrasion of the skin

The course of the disease is variable the average duration of facial erysipelas being given as four days by Pontano[17] as eight days by Lenhartz[1] The onset usually is abrupt with chill and fever and at about the same time the erythema appears usually near the nose Less commonly it starts from the ears in connection with otitis media the operative wound in mastoiditis or a chronic eczema of the external ear

Once started it spreads rapidly over the nose and cheeks often in butter fly fashion The appearance of the face is then quite characteristic The skin is greatly swollen red and frequently the site of bullæ The eyes often are closed from edema of the lids and the ears are swollen stiff and red The margin of the inflamed area is sharply marked and usually raised forming the so-called wall This depends upon the structure of the skin however for where it is loose no wall is seen and edema is marked as in the eye lids and scrotum The chin usually escapes Frequently small tongue like pink pro

the streptococcus in the skin lesion and reproduced the disease by the inoculation into the skin of pure cultures

Etiology

Erysipelas takes place invariably from the infection of a wound This is obvious in surgical cases In the ordinary facial erysipelas infection takes place through minute abrasions or fissures, which often have healed by the time the patient consults a physician In other cases such as those occurring in connection with excoriations about the nose the source is apparent It is seldom contracted from another case of erysipelas but usually from streptococci of other origin A recent streptococcic inflammation of the tonsils paranasal sinuses or ears often is the source of infection of the skin Erysipelas starting from the operative wound is not uncommon after mastoidectomy

Erysipelas is more common in the colder seasons of the year, especially in late winter and in spring when streptococcic inflammations in general are most rife Women and men are affected in about equal proportions The age incidence is quite different from that of scarlet fever as shown by Blake[6], being high in the first two years of life and then falling sharply to rise again after middle age, reaching its peak between the ages of 35 and 60

Predisposing Causes — Chronic cachectic states alcoholism exposure to cold and fatigue predispose to the disease Women are especially susceptible at the time of menstruation One attack does not confer immunity, in fact erysipelas is perhaps the disease most frequently showing recurrences which are estimated to occur in twenty per cent As many as forty attacks have been observed in one patient but usually not more than two or three

Bacteriology

It has been conclusively proved that erysipelas is due to infection of the skin with β streptococci Fehleisen believed that a specific strain, *Streptococcus erysipelatis*, was involved and Birkhaug[5] in 1925 published researches which appeared to show that this was the case but more recent work by Francis[9] Spicer [1] and others indicate that the erysipelas group is quite comprehensive and overlaps other groups of β hemolytic streptococci In general this group shows relatively low toxin producing capacity in contrast with what obtains in scarlet fever Occasionally erysipelas has followed scarlet fever and has been shown by agglutinin absorption tests to have been due to the scarlet fever group of streptococci

Very rarely cases have been reported in which the staphylococcus apparently was the causative organism

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The streptococci are found almost exclusively in the lymphatic vessels of the skin They are most numerous at the margin of the inflamed area and are absent in the central part The exudate consists very largely of serum and small mononuclear cells The internal organs show the usual changes met with in acute infectious diseases viz cloudy swelling and fatty infiltration of the heart liver and kidneys and acute splenic tumor The splenic enlargement is very moderate in extent A terminal bronchopneumonia often is present

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jections are seen at the periphery Almost always extension takes place by continuity and where this is apparently not the case, close inspection will reveal small red threads representing the lymphatics connecting the two areas

Frequently the forehead becomes involved but the process usually stops at the hair line In about twelve per cent of facial cases the inflammation extends to the scalp and then usually does not stop till it reaches the nape of the neck Occasionally the process extends down the back and may involve the entire body (erysipelas migrans) spreading at one margin while clearing up on the opposite side, in which case the disease may be prolonged fo several weeks or more

The regional lymph nodes always are enlarged but often difficult to palpate Certain situations where the skin is closely attached to the subcutaneous tissues present natural obstacles to the spread of the disease, which either stops there or goes around Such places are the chin and Poupart s ligament

Desquamation of the skin over the inflamed area, of a flaky character, takes place during convalescence Surgical erysipelas may start at any part of the body The vulva occasionally is the starting point in puerperal women and then there is danger that the disease may extend into the vagina and cause puerperal infection often fatal More often, however, erysipelas in the puerperium runs its customary course

The usual symptoms of toxemia are present in all the more severe cases and delirium is very common even in the absence of alcoholism It is stated by many writers that fever often is absent some putting the afebrile cases as high as twenty five per cent I must agree with Lenhartz that this statement is due to errors of observation Of 127 cases seen during the acute stage I observed an afebrile course in only two one of these was a cachectic patient with cancer of the gall bladder, in the other the inflammation remained restricted to an area the size of a silver dollar

The fever frequently is high, it may be continuous more commonly it is remittent rarely intermittent The cases with continuous fever are apt to end with a crisis Since complications are not common, the temperature chart affords a very good guide to the progress of the disease, a fresh rise of temperature after a fall almost always indicating a lighting up of the process Relapses are not uncommon occurring in from five to ten per cent

Leukocytosis is the rule The spleen usually is not palpably enlarged The urine shows a febrile albuminuria but true nephritis is not common Urobilin often is present Hirsch[12] has noted the presence of nystagmus on lateral motion of the eyes as a constant and early symptom, which disappears with the fever and considers it an important diagnostic sign absent in other febrile conditions It should be noted however, that it is very common in

trench fever, and perhaps it would be found in other conditions if looked for

Blood cultures almost always are negative in cases that recover Sprunt[22] found the streptococcus in the blood in life in five of thirty seven cases four of which died while all of the cases with negative blood culture recovered

Unlike scarlet fever erysipelas is a disease which is very prone to recurrence From fifteen to twenty per cent of patients give a history of one or more previous attacks and in rare instances the disease recurs with great frequency

Erysipelas of the Mucous Membranes

This is a rare event The process may start in the throat which becomes a fiery red color greatly swollen and very painful It then extends to the skin Or it may start on the skin and extend through the nose or mouth to the throat The larynx may become involved with imminent danger of suffocation A primary erysipelas of the larynx has been described but since it never extends to the skin the diagnosis must always remain doubtful

Atypical Forms

Under the title latent erysipelas Berger[4] and Schlesinger[19] have described cases in which the initial symptoms were infiltration of the subcutaneous tissues followed after a period varying from a week to two months by typical erysipelas of the skin over the infiltration the latter rapidly disappeared after the onset of the erysipelas Rarely in cachectic individuals an otherwise typical erysipelas shows a white or pale pink color instead of red, anemic erysipelas

THE INFLUENCE OF ERYSIPELAS ON PRE EXISTING CHRONIC DISEASE

Occasionally malignant growths undergo a marked recession after an attack of erysipelas a fact that led Coley to introduce his method of injecting the toxins obtained from filtering a mixed growth of streptococci from erysipelas and *B prodigiosus* into patients with malignant disease This is apparently effective against certain more benign types of osteosarcoma but not against other malignant tumors Lupus of the skin occasionally disappears after erysipelas and Glaser[11] noted the prompt recovery of a severe subacute nephritis after an attack In myelogenous leukemia the leukocyte count may fall to normal after erysipelas but rises before long to the former figure

Complications

The commonest complications are subcutaneous abscesses which occur in five per cent They are situated most frequently in the eyelids Gangrene of the skin is sometimes seen, usually in the legs in association with varicose ulcers I have seen it develop at the external ear with recovery Suppurative lymphadenitis may set in Occasionally the nasal sinuses are the seat of suppuration Meningitis by extension through the orbit or from the ear is a rare event Retro-orbital abscess may lead to optic neuritis and loss of sight or rarely to thrombosis of the cavernous sinus Pericarditis and endocarditis are unusual purulent arthritis is very exceptional Pneumonia is not uncommon in severe cases and usually is due not to the streptococcus but to the pneumococcus Occasionally after repeated attacks of erysipelas a chronic swelling similar to elephantiasis, remains

Diagnosis

The diagnosis as a rule can be made at a glance Difficulties arise usually only at the beginning when the lesion is small Acute inflammation of the skin starting from an operative wound and accompanied by fever nearly always is erysipelas In cases of wandering erysipelas of long duration the reaction of the tissues often is slight the color pink instead of red and the sharp line of demarcation lacking In such cases the typical mode of extension will enable a diagnosis From erythema erysipelas is distinguished by the pitting and tenderness on pressure The tenderness is constant over actively inflamed areas and is a valuable indication of extension to the scalp where the skin is hidden by the hair Not infrequently a spreading dermatitis occurs in the neighborhood of ulcers and may resemble erysipelas Usually it can be distinguished by the lack of a wall and by the presence of lymphangitis showing as reddened streaks proximal to the inflamed area

Erysipeloid as its name implies bears a certain resemblance to erysipelas It is due to the organism of swine erysipelas *Erysipelothrix rhusiopathiæ* otherwise called *Bacillus erysipelatis suis* In Germany and France owing to the prevalence of swine erysipelas it is fairly common as an occupational disease among butchers veterinarians and persons handling meat, game and fish In England and the United States where swine erysipelas is much less common erysipeloid is rather rare and a large proportion of the cases are derived from fish In the United States Klauder Richter and Harkins[15] found it very frequently among fishermen handling live fish in fish pounds, and Gilchrist[16] has reported a large number of cases occurring on the shores of Chesapeake Bay as a result of crab bites The disease almost invariably is situated on the

hands and follows inoculation of a small wound with the causative organism It is distinguished from erysipelas by the absence of fever and of constitutional symptoms by the color of the affected skin which is bluish red instead of bright red and by the slow progression with an elevated often scalloped border In the severe form however fever may occur at the onset and lymphangitis and lymphadenitis which are absent in the mild form are frequently noted The diagnosis may be confirmed by cultivating the bacillus from a piece of deeply excised skin (the organisms lie in the corium) or by the prompt curative action of swine erysipelas anti serum For further information the reader should consult an article by Bedford[9] and the excellent critical review by Klauder[1]

Prognosis

Previous to modern chemotherapy the mortality in hospitals was given as from three to eleven per cent It varied with the age and previous condition of the patient being higher in the aged and in infants In the new born up to the age of one month the death rate was very high approximately 90 per cent in the second month it was about half as much and after that it fell rapidly to about the figure for adults Drunkards and persons debilitated by chronic disease were in considerable danger In the young healthy adult the mortality was trifling amounting to only 0 8 per cent in the Prussian army Septicemia and pneumonia accounted for most of the deaths Culotta[7] reported positive blood cultures in all of his fatal cases among infants

Since the advent of chemotherapy the outlook has improved The general mortality has been lowered although owing to the great variation in different statistics it is not possible as yet to give exact figures Most of the severe cases with septicemia now can be saved by the sulfonamides or somewhat more surely by penicillin Even in young infants a comparatively low mortality may be expected

Treatment

The introduction of the sulfonamides and of penicillin has rendered obsolete the older methods of treatment The use of ultraviolet light or of radiation by the x ray is not indicated

Snodgrass and Anderson[27] treated 135 cases with sulfanilamide and at the same time 135 controls with ultraviolet light Twelve of the controls finally were given sulfanilamide because they did so badly There was no spread of the rash after the first 24 hours of treatment and 75 per cent were afebrile after 48 hours Complications occurred in 8 1 per cent of the sulfanilamide series and in 20 7 per cent of the controls

Bergman[8] treated 50 cases with sulfanilamide with 50 simultaneous control

One half of the latter received ultraviolet light, the other half local applications The sulfanilamide series became free of fever sooner, remained afebrile and had only one third the complications occurring in the controls The patients receiving ultraviolet light did no better than those who got local applications only

Other observers depended on statistics of previous years for their controls On account of the variability in the severity of erysipelas from year to year this method is less reliable but the results obtained were so outstanding that there can be no doubt of the efficacy of the sulfonamides For example Hayne, Wolfe and Prim[29] in a series of 162 cases at the Cook County Hospital treated with sulfanilamide reported a mortality of only 2 5 per cent , in previous years it had ranged from 11 to 17 per cent A similar reduction in mortality was noted in the publications of Nelson Rinzler and Kelsey[30] Foley and Yasura[31] and Shank Maxwell and Bozalis[32] The duration of fever and of hospitalization was shortened by several days and the incidence of complications greatly reduced Perhaps the most striking result of sulfonamide therapy has been the recovery of infants with positive blood cultures Bruce and Chalkley[33] have reported on it in infants

Although the published reports up to the present deal only with the use of sulfanilamide it is the general experience that the results obtained with the newer sulfonamides are as good or better with much fewer toxic reactions Sulfadiazine is the drug of choice

The dosage of sulfadiazine is the usual one for streptococcic infections 4 gm (gr 60) as the initial dose and 1 gm (gr 15) every 4 hours thereafter When the temperature has reached normal the dose should be reduced to 1 gm (gr 15) every 6 hours and stopped after 2 or 3 days more

In the case of aged persons and of those with chronic nephritis it is safer to give a smaller initial dose 2 gm (gr 30) and govern subsequent dosage by the blood level Sodium bicarbonate 15 gm (gr 225) daily should be given in all severe cases but is not necessary in those moderately ill and showing a good diuresis

Penicillin is a very effective remedy for erysipelas, but owing to the good results with sulfonamides it seldom is indicated It should be employed in very severe cases with positive blood culture and when toxic reactions occur from sulfonamides For dosage and methods of administration the reader is referred to the section on septicemia

Local applications of warm or cold compresses of boric acid solution or of magnesium sulfate are needed only in severe cases and in the first 24 hours of treatment The general management is that of any acute infection including rest in bed until the temperature has been normal for several days and an easily digested diet with plenty of fluids Hypnotics may be required

In recurrent erysipelas it is important between attacks to treat the chronic eczema ring worm of the feet or ears or sinusitis which are so often the under

lying factors Immunization with autogenous vaccines has not proved satisfactory in my hands

PROPHYLAXIS

Although under ordinary circumstances the danger of transmission to others is not great isolation always should be practised This is more important in hospitals than in the home on account of the greater opportunities for spreading the infection particularly to puerperal and surgical patients and to the new born Surgeons and obstetricians should not come in contact with erysipelas

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CHAPTER XXX

SEPTICEMIA

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SPECIAL FORMS OF SEPTICEMIA

I

Introduction

Septicemia may be defined as a condition in which bacteria are present repeatedly in the blood stream and are productive of symptoms Bacteriemia on the other hand, covers the cases in which bacteria are found in the circulating blood but are not of clinical significance Such a case for example, would be the transitory appearance of streptococci in the blood during the course of an ordinary tonsillitis It is becoming more and more frequent now that the routine taking of blood cultures is practiced to meet with such instances Strictly speaking various specific infections in which bacteria are more or less constantly to be found in the blood should be classified as septicemia e g, typhoid fever, undulant fever pneumonia It is customary however, to exclude such cases from the septicemic group

The use of the term septicemia has been criticized on the ground that it means, literally translated putrid matter in the blood The word was coined in pre bacteriological days and was chosen because so many of the cases were associated with local putrid infections The term has become so firmly rooted in the literature however that it seems unwise to attempt to change it

Certain forms of septicemia were known to the ancients Hippocrates described puerperal septicemia though the nature of the process was not appreciated until the work of Willis (1682) who introduced the name puerperal fever and ascribed it to wounds of the uterus Since then many writers have suggested that it was an infection introduced from without It was the American

author, Oliver Wendell Holmes[1] who was the first to prove that the infection might be carried from patient to patient by doctors and midwives His publication attracted little attention however and it is to Semmelweiss[2] that the chief credit for demonstrating the usual origin of puerperal infection is due

The history of wound infection is somewhat similar Known and described by Hippocrates and Celsus and ascribed by Avicenna (1000 A D) to decomposition of wounds and putrefaction of the blood, it was not until modern times that a true conception of the process was attained John Hunter in 1774 showed the association of pyemia with suppurative phlebitis Virchow[3] in 1856 demonstrated in a masterly manner the part played by suppurative phlebitis and infected emboli and was the first to distinguish clearly between septicemia and pyemia

The foundation of modern bacteriology and of the scientific study of septicemia was laid by Pasteur[4] who proved that fermentation and putrefaction could occur only in the presence of microorganisms and subsequently made many important contributions to the subject of the septic diseases Koch[5] working with putrid fluids demonstrated the difference between toxemia and septicemia Leube[6] in 1878 was among the first to recognize the fact that septicemia might occur in the absence of wound infection and introduced the term cryptogenetic septicopyemia to cover this condition

Classification

It is customary to speak of primary septicemia where the condition occurs in the absence of one of the specific infectious diseases while the term secondary septicemia is employed where the blood infection occurs as a complication of such diseases as in scarlet fever Where more than one kind of bacterium is present in the blood it is called a mixed infection

Septicemia may be further classified according to the kind of organism present in the blood or according to the clinical features The former method appeals more to the modern desire for an etiological nosology but is at times difficult of application The latter is of advantage where it is not possible to determine the causative organism Often a combination of the two is more descriptive e g post partum infection with streptococcic septicemia

In this article first we shall describe septicemia in general and then take up separately the infections with the various bacteria finishing with a description of certain special types of septicemia

Bacteriology

The organisms found in the blood stream usually are the same as those in the local inflammatory process from which the general infection is derived

When however, there is a mixed infection at the original focus it is the usual rule that only one kind of bacterium is found in the circulating blood Formerly it was believed that little reliance could be placed on post mortem cultures and that in the case of the colon bacillus in particular an agonal or post mortem invasion of the blood was the rule

These results however were due to faulty preservation of the cadaver, for Simmonds[7], in a series of 1 200 autopsies, found the colon bacillus in the blood in only 8 per cent and chiefly in cases in which there was disease of the alimentary or genitourinary tract In general, the results of post mortem blood cultures agree very well with those obtained during life except that the number of colonies is much greater owing to multiplication during the last hours of life when the defenses of the body against infection have broken down In those cases with negative blood culture during life in which a positive culture is obtained after death the organism obtained usually is the same as was to have been expected from the nature of the primary focus

Terminal Infections

The question of terminal infections may be considered here because they are of more bacteriological than clinical interest As Osler aptly remarked "there is truth in the paradoxical statement that persons rarely die of the disease with which they suffer A large proportion of the cases with chronic and incurable affections are carried off by terminal infections Thus Flexner[8] found in 255 cases of chronic disease of the heart and kidneys terminal infection, excluding tuberculosis in 213 or 84 per cent In the majority of positive cases the infection was local not generalized Terminal septicemia occurred in 52 cases or o per cent of the whole number The frequency of these infections is doubtless due to the lowered resistance to bacterial invasion which obtains in the late stages of chronic diseases

This was demonstrated by him in the case of the bactericidal power of the blood serum which he found distinctly lowered in most of the cases of chronic disease examined Simmonds[7] out of 1 200 consecutive autopsies found positive blood cultures in the astonishing proportion of 48 per cent and in 95 per cent of these only one sort of bacterium was demonstrated He did not make anaerobic cultures That these were not instances of post mortem invasion was shown by the consistently negative results in chronic afebrile disease of the heart and arteries in acute tuberculosis not involving the lungs in chronic polyarthritis etc These terminal infections occur in the last few days of life and are manifested as a rule only by fever increasing apathy and stupor Their presence may be inferred and the diagnosis suspected under these circumstances and confirmed by the results of blood cultures

Relative Frequency of Different Bacteria

The streptococcus is by far the most common organism to cause septicemia with the staphylococcus next followed by the pneumococcus and the colon bacillus The statistics vary somewhat with the nature of the hospital material Thus Lenhartz[9] with a medical and puerperal material found during life the streptococcus in 61 per cent the staphylococcus in 17 per cent the pneumococcus in 14 per cent and the colon bacillus in 5 per cent Warren and Herrick[10] from a medical clinic reported streptococcus 54 per cent staphylococcus 31 per cent pneumococcus 8 per cent colon 5 per cent mixed infections 5 per cent Bertelsmann[11] working with surgical material found the same proportion of streptococci (56 per cent) staphylococci in 31 per cent but pneumococci in only 4 per cent

The results of post mortem cultures are similar Thus Simmonds[7] found the streptococcus in 63 per cent the pneumococcus in 18 per cent colon bacillus in 17 per cent and staphylococcus in only 6 per cent The smaller proportion of staphylococcal infection is accounted for by the fact that many of his cases were terminal streptococcal infections which usually do not figure in clinical reports

Numerous other organisms are met with occasionally but not often enough to be represented accurately in percentages Among these the more important are the gonococcus the meningococcus the gas bacillus the influenza bacillus and the bacillus pyocyaneus Still more rare are blood infections with the bacillus of anthrax of diphtheria with micrococcus tetragenus bacillus proteus bacillus alkaligenes etc

Technique for Taking Blood Cultures

The technique for taking blood cultures is as follows Withdraw approximately 9 c c of blood from an arm vein by needle and syringe Place in a bottle containing 50 c c of a nutrient broth and mix thoroughly Add 1 c c and 2 c c of blood to two tubes containing 10 c c of melted nutrient agar which is at a temperature of not over 45 C Mix the blood and agar thoroughly and pour each tube s contents into Petri plates When hardened the plates and bottle are incubated at 37° C and examined for growth every 24 hours No specimens are discarded as negative until after at least ten days observation

When anaerobic cultures are desired duplicate samples are made One portion is then placed in an anaerobic jar either in a vacuum or increased carbon dioxide tension The other portion is incubated at normal oxygen tension

PATHOLOGY

The most striking gross changes are in the spleen which is almost always enlarged and often is very soft the pulp presenting the so-called dregs of paint

appearance In other cases it is firm with greatly enlarged follicles The viscera present well marked cloudy swelling, sometimes accompanied by fatty change The aorta and larger arteries are stained by hemoglobin Frequency small hemorrhages are found, particularly in the pleura and pericardium and in the skin

Histologically besides the changes due to cloudy swelling and fatty infiltration focal necrosis is not uncommon, especially in the liver The hemorrhagic areas usually show the presence of bacteria but are due chiefly to alterations in the walls of the capillaries rather than to emboli In many cases no other lesions are found and the post mortem diagnosis is dependent upon the bacteriological examination

In cases with metastases however, the picture is much more varied Here multiple embolism has occurred either by means of fragments of blood clot or of the vegetation from diseased heart valves or from masses of bacteria Small infarcts are produced which usually go on to abscess formation The latter however is by no means a necessary result depending partly on the nature of the infecting organisms Thus the infarcts caused by the streptococcus viridans never suppurate, though they may be swarming with bacteria On the other hand staphylococcal emboli always cause abscess formation

Metastases may be found in one or more of the following structures lungs spleen liver kidneys, brain subcutaneous tissues muscles, myocardium skin intestines and bones For further information about metastases the reader is referred to a following section on pathogenesis

Hematogenous infection of serous cavities is not uncommon especially of the joints pericardium meninges and pleurae occasionally of the peritoneum

Etiology

Septicemia affects all ages from the cradle to old age and both sexes with about equal frequency Predisposition to infection is furnished by chronic debilitating diseases of all sorts anemia per se seems to be favorable to infection as indicated by animal experiments and clinical experience In healthy individuals resistance may be decreased temporarily by hunger, thirst fatigue, lowering of the body temperature by exposure to cold or by psychic factors such as worry and grief There are also otherwise robust persons who are peculiarly susceptible to infection presumably by reason of a paucity of immune bodies in their blood This may be an inherited character for one meets with families in which there is a marked proneness to suffer from infectious diseases

Pathogenesis

For septicemia to take place two requisites must be fulfilled (1) there must be a ' portal of entry by which the bacteria enter the body and (2) there must

be a septic focus ("Sepsisherd" of Schottmüller), which is in communication either with the blood stream or with the lymphatics. From this focus bacteria pass into the blood either constantly or intermittently. In case the primary septic focus becomes inactive recovery may ensue or a secondary septic focus *may be set up by means of metastasis and the process may even go on to the formation of a tertiary focus in communication with the blood stream*

The Portal of Entry

Infection may take place from a suppurative process or infected wound in any part of the body. The so-called cryptogenetic septicemias in which no source of infection is discoverable have become uncommon now that the importance of minute abrasions wounds and fissures of the skin eczema impetigo inflammatory processes of the tonsils teeth respiratory and genitourinary tracts has been realized. The relative frequency of the different portals of entry is impossible to determine with accuracy on account of the lack of reliable vital statistics. Judging from hospital material the most common are infected wounds of the skin and underlying structures next come puerperal infections and lastly localized inflammatory processes

Lacerated and contused wounds especially if associated with compound fractures and wounds with deep pockets are the kind most often involved. The appearance of the wound may be characteristic the surface is dry and discolored and shows no pus or granulation tissue. The presence of putrefactive bacteria in the wound appears to enhance the virulence of the pyogenic cocci and thus facilitates a general infection by the latter. Occasionally bed sores and other chronic ulcers are the source of the trouble

The mode of infection in puerperal fever will be discussed in the section on puerperal septicemia. Under localized inflammatory processes come a great variety of local foci. Infections starting from the skin and subcutaneous structures arise oftenest from boils, carbuncles and felons from phlegmons and suppurations of the tendon sheaths. The respiratory tract is a frequent source of infection especially the tonsils less often the accessory sinuses of the nose and the lungs. Ears and teeth also rank high. The genitourinary tract often furnishes a portal of entry especially in the form of cystitis and pyelitis prostatic abscesses and strictures of the urethra less often disease of the female genitalia in the absence of pregnancy. Inflammatory disease of the intestine both with and without ulceration and infection of the biliary passages are occasional sources of septicemia. Peritonitis and pleuritis do not originate septicemia though often they are a result of it. Appendicitis occasionally leads to suppurative pylephlebitis with abscesses of the liver following phlebitis of the appendiceal or ileo-colic vein but bacteriemia is seldom noted the liver acting as an efficient filter. Schott

appearance In other cases it is firm with greatly enlarged follicles The viscera present well marked cloudy swelling sometimes accompanied by fatty change The aorta and larger arteries are stained by hemoglobin Frequency small hemorrhages are found particularly in the pleura and pericardium and in the skin

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Pathogenesis

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Metastatic abscesses arise when infected emboli or large masses of bacteria are carried by the circulating blood to other parts of the body Such an abscess may gain access to the blood stream and thus constitute a further source of septicemia which may continue to operate after the original focus has ceased to be effective primary and secondary focus of Schottmuller

According to the important researches of Nathan[14] of the Hamburg school the metastasis is situated in that part of the circulation in which there is a septic focus That is to say if the metastasis is situated on the arterial side there is a septic focus in the pulmonary veins the left side of the heart or very rarely in the larger arteries bearing in mind the fact that the pulmonary veins carry arterial blood If the primary focus is on the venous side the first metastases occur in the lungs and may remain restricted to these organs In case however infective phlebitis of the pulmonary vein leading from the metastatic abscess takes place this becomes a secondary septic focus and may give rise to metastases on the arterial side A primary septic focus may occur in the lungs but this is not often the case If there is an open foramen ovale bacteria may pass through it from the right to the left side of the heart and thus reach the arterial circulation or a septic endocarditis of the left side may be the source of arterial emboli Nathan was able to demonstrate septic thrombosis of a small pulmonary vein in almost all cases with metastases on the arterial side with the exception of those in which a patent foramen ovale or a septic endocarditis explained the situation In some cases both thrombosis of a pulmonary vein and open foramen ovale or endocarditis were present

Clinical Description of Septicemia

The course of septicemia is so varied that it is difficult to draw a picture that will fit all cases Without regard to the kind of bacterium present the course may be either fulminating acute subacute or chronic In the fulminating cases the patient is very ill from the beginning The symptoms are those of a violent toxemia and vary according to the system most involved In some the cerebral symptoms predominate and delirium stupor and coma or the signs of meningismus make up the picture In others the mind is clear and the signs of circulatory collapse prevail In still others vomiting diarrhea and abdominal pain are seen The fulminating type invariably ends fatally in the course of a few days

Often however the course is more prolonged lasting from two to four weeks In this type the symptoms of toxemia prevail both in the cases with and without metastases In the former local signs may be present indicating the occurrence of metastases or they may be lacking The face has a septic look a combination of apathy and pallor Headache and pains in the bones muscles or joints are common Delirium is frequent especially at night The patient may pass into

muller and Bingold[1] however state that blood cultures often are positive in such cases provided that anaerobic methods are used Acute or chronic osteomyelitis may give rise to infection of the blood stream

The paths of infection vary with different bacteria Thus the staphylococcus enters usually from the skin fairly often from the uterus in the case of septic abortions seldom from the upper respiratory tract, the colon bacillus comes from the intestine directly or indirectly from the genitourinary tract or gall bladder the gonococcus from the genitourinary tract the streptococcus is a common invader from either skin or mucous membrane The lesion at the portal of entry furuncle tonsillitis etc may have healed completely before the onset of septicemia

After the bacteria gain access to the blood stream they are acted upon by the various antibacterial bodies therein and are finally removed by the organs of the reticuloendothelial system liver spleen bone marrow etc where they undergo phagocytosis For this reason a single infection of the blood stream rarely leads to septicemia there may be a chill and a brief period of fever, and then recovery sets in Often indeed such a temporary bacteriemia occurs without any symptoms other than those attending the local inflammation

The Septic Focus

If septicemia is to occur bacteria must gain access to the blood stream either directly by way of a vein or indirectly through the lymphatic system The site of this is known as the septic focus It may be situated at the portal of entry more commonly it is in the vicinity sometimes it is at quite a distance

If the infection takes place by the venous route usually there is a suppurative thrombophlebitis either of a small vein in the neighborhood of the initial lesion or of a larger vein in its drainage area Penetration of the vein by bacteria often occurs without gross perforation and thrombophlebitis follows either occlusive or much less commonly in the form of mural phlebitis

In the case of infection by way of the lymphatics the septic focus may be an abscess which perforates into a lymphatic vessel or it may be a suppurating lymph node Thence the bacteria must pass through the intervening lymph nodes if any and so to the thoracic duct and the blood stream Sometimes however the infection is only apparently by way of the lymphatics for a suppurating lymph node may discharge its contents into an adjacent vein Very rarely bacteria may pass directly into the thoracic duct from a septic focus as in the case of von Clahn[13]

Of these two paths of infection that by way of a vein is much the more common The staphylococcus usually invades in this manner while the streptococcus may choose either route

The liver often is moderately enlarged as a result of cloudy swelling Jaundice is *not uncommon and is of the non obstructive type with stools of normal* color Usually it is not an indication of the presence of hepatic metastases but is due to diffuse changes in the liver or more rarely to hemolysis Metastases usually are small and multiple in which case they do not give rise to physical signs or symptoms except enlargement of the liver which may remain within moderate bounds Occasionally as in the case of septicemia due to Buday s bacillus the usual signs of hepatic abscess may be found jaundice shoulder pain localized tenderness x ray findings

The spleen is almost always enlarged but often it is so soft that it is not palpable The most marked enlargement is met with in subacute bacterial endocarditis Not infrequently it is the seat of infarcts either bland or suppurative and then perisplenitis usually takes place accompanied by pain and tenderness and sometimes a friction rub Very rarely an abscess of the spleen bursts into the peritoneal cavity or thrombosis of one of the branches of the splenic vein may lead to pylephlebitis

The kidneys often are involved in one way or another Febrile albuminuria is the rule Acute nephritis occasionally develops with blood granular and epithelial casts and an increased amount of albumin in the urine The multiple small abscesses which are so common in staphylococcic septicemias do not give rise to symptoms nor to pyuria but the causative organisms may be recovered from the urine Larger infarcts may give rise to pain and tenderness over the kidney and to hematuria Pyelitis secondary to septicemia is of rare occurrence Occasionally pyelonephritis constitutes the primary septic focus in which case obstruction of the urinary passages usually is present as a contributory factor

The skin often is the site of lesion which are of great diagnostic value Eruptions are encountered frequently The most common occurring in about 50 per cent of all cases is the petechial rash This appears in the form of small hemorrhages in the skin or mucous membranes usually not numerous sometimes very abundant The palms and the palpebral conjunctiva are favorite sites but any part of the body may be affected Erythematous rashes also are frequent in the form of fleeting diffuse blushes usually of moderate extent sometimes involving large areas Very rarely in our experience do they closely simulate the rash of scarlet fever in their distribution and punctate appearance In chronic meningococcus septicemia a papular rash often resembling erythema multiforme or erythema nodosum usually is present This eruption recurs many times with renewed bouts of fever and with the unusual temperature chart which often shows tertian or quartan phases interposed between periods of quotidian fever constitutes a characteristic clinical picture (Dock[15] personal observation)

Another form of eruption met with especially in staphylococcus infections consists of pin head to pea sized vesicles with a red areola the contents of which

a "typhoid" state The fever usually is high and the pulse rapid Repeated chills are seen frequently in the cases with intermittent fever and usually are associated with purulent metastases or with endocarditis in the latter case they occur at the time of the breaking off of emboli with the consequent liberation of bacteria in large numbers

The subacute and chronic cases last from one to several months, sometimes a year or longer The symptoms are less violent than in the acute form, and death takes place finally from exhaustion, anemia and prolonged intoxication, or recovery with a protracted convalescence ensues The onset usually is acute with chills and fever If there is already fever as a result of the local process, there is a sudden rise in temperature often with chills In some cases the onset is gradual the height of the fever not being reached for several days

The temperature usually is high The type varies greatly not only in different infections but in the same case from time to time Certain bacteria show a marked tendency which however is far from invariable to show definite types of temperature chart Thus the acute staphylococcic septicemias usually show a high continuous or slightly remittent curve, while those due to the gonococcus and the colon bacillus tend to have an intermittent or highly remittent one The streptococcus infections show no constant type there is a tendency to the intermittent and remittent forms but continuous fevers are not uncommon Chronic meningococcus septicemia as shown by Dock[15] and others is accompanied by an intermittent fever lasting several months and often showing the tertian or quartan form like that of malaria As the fatal termination approaches, the temperature may fall to normal with symptoms of exhaustion or, particularly in acute septicemia hyperpyrexia may occur In prolonged cases short periods of normal or of subfebrile temperatures may be interposed

The pulse usually is rapid 120 to 140 or more In some cases it is less elevated and occasionally a well marked bradycardia is noted, in a personal case of streptococcic septicemia the relatively slow pulse aroused a suspicion of typhoid The heart usually is not enlarged unless as a result of antecedent disease Even in the presence of acute endocarditis dilatation is the exception, and congestive heart failure is a rarity Mitral systolic murmurs are common and can be accounted for in the absence of a lesion of the mitral valve by the fever and the anemia Diastolic murmurs are much less frequent and indicate, with rare exceptions the presence of endocarditis

Cases with much toxemia may show a rapid respiratory rate Usually however the presence of dyspnea indicates involvement of the lungs or pleura Bronchopneumonia is not infrequent Metastases in the lungs usually are bilateral and often numerous they do not as a rule give rise to distinctive signs but only to cough and dyspnea and perhaps to râles distributed in a patchy manner Pleurisy and empyema may occur

cerebral abscesses sometimes are present chiefly in staphylococcus septicemia Headache dizziness delirium stupor and coma are common features as a result of toxemia but convulsions in adults indicate an organic lesion

Of the serous membranes the joints most frequently are involved Often this happens early in the disease and is mistaken for rheumatic fever The larger joints usually are the ones affected and show all gradations from a simple arthralgia to serous and purulent effusion The skin often is reddened and the periarticular tissues involved in the process

Pericarditis is not uncommon especially in staphylococcic infections Though frequently overlooked during life in our experience a friction rub is almost always to be detected if frequent examinations are made If life is sufficiently prolonged the process goes on to serous or purulent exudation *Peritonitis is common in* postpartum infections and here is usually the result of extension from the local process Occasionally it is due to hematogenous infection

Pain in the bones especially the long bones is a common feature in septicemia and is due usually to the presence of bacteria In some cases it is fleeting in others the pain is referred to one spot and accompanied by local tenderness indicating an acute periostitis This occasionally goes on to suppuration Inflammation of the bone marrow may occur in the case of all of the pyogenic bacteria but is not common except in primary osteomyelitis a condition that will be described later under the heading staphylococcic septicemia

The testes and epididymis occasionally are the site of metastatic abscesses

Changes in the blood are frequent Leucocytosis is common but far from invariable According to Schottmuller and Bingold[1] usually there is no leucocytosis except for a brief period after chills and when abscesses are forming In the case of septicemia due to the gas bacillus however a high grade of leucocytosis is the rule The polynuclear neutrophiles are increased usually with a shift to the left Rarely in subacute bacterial endocarditis macrophages histiocytes are present in large numbers these are very large cells with bizarre shapes owing to their active ameboid motion

Agranulocytosis and septicemia may be associated in which case agranulocytosis often is the primary and septicemia the secondary event Much more frequently a moderate leucopenia with predominance of polynuclears is met with

Anemia of a moderate degree is the rule In gas bacillus infections however *a tremendously rapid fall in the number of red cells may take place* the result of hemolysis A high grade of anemia but of gradual development occasionally occurs in septicemia due to the hemolytic streptococcus the anaerobic streptococcus putridus or the staphylococcus In such cases numerous nucleated red cells may be found and rarely the blood picture of pernicious anemia may be simulated

Thrombocytopenic purpura occasionally occurs as a secondary manifes

soon become purulent Occasionally, as in the streptococcic case described by Churchman[16] large bullæ appear, the contents of which are clear at first but rapidly become hemorrhagic Ordinary herpes of the lips is not uncommon and is especially frequent in colon bacillus infections, in which it is sometimes remarkably profuse and may extend to the mucous membrane of the mouth (Schottmuller and Bingold[1] personal observation) Nodular subcutaneous infiltrations may appear the overlying skin becomes reddened and suppuration may take place but not invariably Occasionally urticarial papular or pustular eruptions are seen Peculiar pustular necrotizing lesions appear in pyocyaneous septicemia, described later

Jaundice is a fairly frequent event irrespective of the kind of bacterium As noted above it does not as a rule indicate metastasis to the liver nor is it often a sign of secondary involvement of the gall bladder or bile passages though hematogenous infection of the gall bladder has been reported, it is decidedly a rarity except in the case of typhoid fever Even if intense the jaundice of septicemia does not lead to decolorization of the stools usually it is the result of diffuse changes in the liver much more rarely it is due to hemolysis A peculiar type of jaundice often is present in septicemia caused by the gas bacillus the skin assuming a bronzed color owing to the presence in the plasma of products of hemolysis oxyhemoglobin methemoglobin hematin in varying proportions

The subcutaneous tissues frequently are the site of metastatic abscesses Abscesses in the muscles also are not uncommon but usually do not give rise to symptoms except in subacute or chronic cases in which they may become large enough to be recognized and opened

Retinal hemorrhages are very common being met with at some time during the disease in about one third of the cases They are of great diagnostic importance since they seldom occur in those febrile diseases which are likely to be confused with septicemia Occasionally a whitish spot is seen in the center of a petechia this is due to necrosis and is not to be confused with 'Roth's spots' which are pure white without any indication of hemorrhage These Roth's spots are much rarer than petechiæ but when present they constitute a valuable diagnostic sign Panophthalmitis is a rare form of metastasis, it is bilateral in one third of the cases It occurs most frequently in streptococcic septicemia and in some epidemics of meningococcic meningitis It leads to loss of vision and in case of recovery to shrivelling of the eye ball phthisis bulbi Optic neuritis may occur particularly in subacute bacterial endocarditis

Meningitis of hematogenous origin is very frequent in penumococcus septicemia and as a late event in chronic meningococcus septicemia it sometimes occurs in other forms Symptoms of meningeal irritation meningismus may occur in the absence of inflammatory changes in the spinal fluid Cerebral embolism often happens in cases with associated endocarditis Small multiple

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tation in septicemia, in other instances purpura is the primary disease and septicemia a complication

DIAGNOSIS

Septicemia is to be suspected in all cases with fever and marked constitutional involvement following wounds or local inflammatory processes and in continued fevers of obscure origin particularly if repeated chills are present The routine employment of blood cultures is of the greatest value but since these are sometimes negative at first the older methods of diagnosis still hold their importance While a persistently negative blood culture speaks against the diagnosis of septicemia it should be borne in mind that certain bacteria are difficult to cultivate and require special media, meningococcus, gas bacillus, etc Moreover, the time at which cultures are taken matters the results often being negative after a chill or with a falling temperature The best time is when the temperature is rising shortly before a chill

A careful history and thorough physical examination are here, as in all obscure diseases, a sine qua non of successful diagnosis An especial search should be made for a possible focus of infection which often lies in the skin in the shape of an infected wound a furuncle carbuncle or other more trivial infection Examination of the ears tonsils, genitourinary tract, etc may reveal the origin of the trouble

The points of chief diagnostic value lie in the localized rather than in the general manifestations They are principally arthritis endocarditis skin rashes, retinal hemorrhages, embolic phenomena, metastatic abscesses and inflammatory conditions of the bones

In differential diagnosis the chief diseases to be considered are acute rheumatic fever typhoid fever miliary tuberculosis, tularemia, undulant fever and localized infections with marked constitutional signs Less often the question of scarlet fever or of malaria arises

Rheumatic fever has in common with septicemia the joint involvement and endocarditis In favor of rheumatic fever are the characteristic sweats the fleeting involvement of one joint after another and the favorable effect of salicylates The affection often is monarticular in septicemia never in rheumatism A fleeting involvement of the joints may occur, however in the early stages of septicemia and since the effusion in such cases usually is sterile (Lenhartz) the resemblance to rheumatism may be very close The occurrence of suppuration in a joint positively excludes the diagnosis of acute articular rheumatism The presence of intermittent fever with repeated chills is strongly in favor of septicemia Petechiæ of the skin or retina embolic phenomena and metastatic abscesses are common in septicemia absent in rheumatic fever Blood cultures in the latter are almost consistently negative

The clinical resemblance between typhoid fever and septicemia often is quite close. The occurrence of typical rose spots or of intestinal hemorrhages speaks strongly for typhoid fever, though the former has been reported in a few instances of septicemia. The leucopenia of typhoid is suggestive but does not positively exclude septicemia. The differential count, however, almost always permits of a conclusion, lymphocytosis being the rule in typhoid and exceedingly rare in sepsis. The results of the Widal examination and of blood, stool and urinary cultures will render the diagnosis certain.

In favor of acute miliary tuberculosis are the dyspnea and cyanosis out of proportion to the physical signs in the pulmonary type of this disease, and the finding of active tuberculous lesions somewhere in the body. The characteristic mottled appearance of x-ray films of the lungs renders the diagnosis clear and may be present in the meningitic and the typhoid as well as in the pulmonary form. In infants the presence of skin tuberculides is very helpful in diagnosis. Miliary tubercles in the choroid are decisive if demonstrated, but usually they occur too late in the disease to be of much assistance. Tubercle bacilli are rarely to be found in the sputum; sometimes they are present in the urine and always should be searched for. Leucopenia with increase of the polynuclears is common in miliary tuberculosis, rare in septicemia. A high total count, however, may occur in the former, especially in the meningitic form. The results of lumbar puncture are conclusive in the meningitic form of miliary tuberculosis. The occurrence of petechiae, embolism, joint involvement and purulent metastases render the diagnosis of septicemia certain, while endocarditis and retinal hemorrhages may occur, though very rarely, in tuberculosis.

Tularemia should be thought of when fever occurs in persons who have recently dressed wild rabbits or have been bitten by ticks or flies in regions where this disease is prevalent, or in laboratory workers who have been handling animals infected with *B. tularense*. The ulcero-glandular type is recognized by the presence of a primary lesion, a punched-out ulcer, at the site of infection with marked and persistent swelling of the regional lymph nodes, often going on to suppuration. In the oculo-glandular type there is a primary lesion in the conjunctiva, usually becoming ulcerated and accompanied with marked swelling of the eyelid and of the preauricular and cervical lymph nodes. In the glandular type there is a marked generalized enlargement of the lymph nodes and of the spleen without any local lesion at the portal of entry. The typhoidal type occurs almost exclusively in laboratory workers and shows only fever of two or three weeks' duration without either primary lesion or enlargement of the lymph nodes. The pneumonic form is more like pneumonia or tuberculosis than septicemia. The clinical diagnosis of tularemia may be confirmed by agglutination tests, bearing in mind the not infrequent cross agglutination with the Brucella group, or by the results of inoculation of the patient's blood or material from the

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with much higher figures for the staphylococcus the streptococcus and the pneumococcus At the present time it is difficult to give exact figures but it is probably safe to say that the mortality is now less than 30 per cent

Many of the fulminating cases die but some of them can be saved by chemotherapy Excellent results with penicillin are being obtained in subacute bacterial endocarditis for a discussion of which the reader is referred to the section on this disease

As in other diseases for which specific drugs are available the prognosis is best in those cases which are treated early and a prompt bacteriological diagnosis is therefore of prime importance

The outlook is worse in those of advanced years and in persons with serious chronic diseases such as carcinoma heart failure and chronic nephritis Recovery however is not unusual among the aged

TREATMENT

The treatment of septicemia is primarily medical and has as its main object the sterilization of the blood stream by means of chemotherapy Surgical measures may be required as in the treatment of the primary focus and of metastatic abscesses

General Measures

These are directed largely to supporting the strength of the patient and aiding in the elimination of toxins Rest in bed and good nursing are essential The diet should be bland and nutritious A high calory diet certainly is in place if the state of the digestive tract is good This may be attained by the use of cereals toast milk cream sugar and eggs If only liquids can be taken they can be enriched by the addition of milk sugar cream in small amounts and raw eggs The number of raw eggs should not exceed three or four in the twenty four hours as eggs in the raw state may cause diarrhea

Fluids should be forced up to a point where the diuresis is equal to 1 500 to 2 000 c c per day both with the idea of favoring the elimination of toxins and for the beneficial effect on the mouth and throat Hydrotherapy is of much benefit in controlling insomnia and delirium being superior to drugs for these purposes Tepid sponging or the wet pack are the methods to be employed

Drugs may be needed to control symptoms Occasionally morphine is required for pain or a wild delirium The salicylates may be tried in small doses for the joint pains Digitalis is of no value in the circulatory failure of acute infections and should not be employed unless auricular fibrillation or congestive heart failure is present

primary ulcer or from the lymph nodes into animals Blood cultures require special media

Undulant fever is frequent enough in America to be considered in the case of any fever of obscure origin It has in common with septicemia high fever and frequent involvement of joints It differs in the mode of onset, which is apt to be gradual and in the tendency to remissions and relapses The lack of prostration in some of the milder cases even when the fever is high is a striking feature The blood picture differs from septicemia and resembles typhoid fever in the presence of leucopenia with a reduction of the percentage of polynuclears The diagnosis of undulant fever rests mainly on the positive results of agglutinations tests of skin tests and of cultures of the blood urine and feces

The temperature chart of pyelitis may resemble that of septicemia and localizing symptoms particularly in children may be absent The finding of pus and bacteria usually the colon bacillus in the urine and the localized tenderness over the kidney in front and behind in the costovertebral angle make the diagnosis certain

In cholangitis usually associated with stone in the common duct the daily chills and fever easily may cause confusion Important points are a history of previous attacks of biliary colic varying jaundice of the obstructive type and recurrent attacks of fever the intermittent hepatic fever ' of Charcot Blood cultures usually are negative in cholangitis although bacteriemia probably is often present temporarily at a time immediately preceding a chill

Localized hidden abscesses may cause difficulty, especially in the case of hepatic and perinephric abscess In the diagnosis of the former from septicemia we have found two points of value (1) the higher leucocytosis often reaching 40 000 and (2) the negative results of blood culture Occasionally however, cultures are positive in hepatic abscess, especially in the case of anaerobic infections

Confusion with malaria is possible in the absence of blood examination for plasmodia Leucopenia is present in malaria Osler s dictum that 'any intermittent fever that resists quinine is not malarial is a valuable guide in diagnosis of doubtful cases

Very rarely a scarlatiniform eruption appears in the course of septicemia Such a case may be distinguished from true scarlet fever by the absence of the characteristic changes in the tongue and of desquamation

Prognosis

The prognosis in septicemia formerly very bad has been greatly improved since the introduction of the sulfonamides and of penicillin Previous to these great events the mortality for all forms was in the neighborhood of 60 per cent

more likely to cause toxic reactions Sulfapyridine and sulfanilamide are distinctly inferior and should not be used in this connection

Contraindications — If there has been a toxic reaction to a previous course of one of the sulfonamides it is better to employ penicillin An alternative is to give a sulfonamide different from the one causing the reaction Acute nephritis a not uncommon complication of streptococcic septicemia is not a contraindication but calls for a careful watch of the blood level

Dosage — The usual initial dose is 4 gm (gr 60) followed by one gm (gr 15) every 4 hours This dose is continued until the temperature has been normal for 4 or 5 days after which it is decreased to one gm (gr 15) every 6 hours until the patient has been afebrile for at least 10 days In case of relapse a further course of sulfadiazine is indicated The dosage should be controlled by determinations of the blood level which should be maintained at about 10 mgm per 100 c c of blood In very severe cases it may be advisable to increase the level to 15 mgm per 100 c c of blood but not above this figure

In the fulminating type of septicemia and in the case of those unable to swallow the drug should be given intravenously as the sodium salt the initial dose being 4 gm (gr 60) diluted with 300 c c of saline injected slowly Usually after the initial dose it is possible to give the drug by mouth after an interval of 8 hours If it is necessary to continue intravenous injections they may be given every 8 hours in doses of 2 to 3 gm (gr 30 to 45) adjusted to the blood level or 1 gm (gr 15) every 4 hours if preferred

Administration of Alkali — In order to avoid blocking of the ureters with crystals of the acetylated compound of sulfadiazine it is important that sodium bicarbonate be given It has been shown by Gilligan and associates[17] and by Fox and associates[18] that the solubility of these crystals increases very rapidly after a pH of 7 0 is reached and that crystalluria can be avoided if the urine is kept neutral or alkaline at all times For this purpose a daily dose of 15 gm (gr 225) usually is sufficient it is convenient to give 2 5 gm (gr 37) with each four hourly dose of sulfadiazine

If sulfadiazine is administered by vein it is best that alkali be given with it either as sodium bicarbonate or as sixth molar sodium lactate in the dose of 6 gm (gr 90) Blockage of the ureters has been reported after a single intravenous injection of sulfadiazine given without alkali If dehydration is not present and a good diuresis of at least 1500 cc is maintained the use of alkali may be dispensed with provided that crystalluria is absent

Toxic Reactions — Toxic manifestations are rather frequent occurring in about 10 per cent They include nausea vomiting fever eruptions of the skin and mucous membranes anemia agranulocytosis hematuria blockage of the ureters by crystals hepatitis and cerebral symptoms Of these the commonest are drug fever eruptions and hematuria

Transfusion of blood frequently is employed as an adjunct to chemotherapy Its use is valuable to combat the anemia and also to supply blood platelets in those rare instances where a purpuric state exists from platelet deficiency It is useful also to supply fluid and salts when these are deficient, but this can be done as well in most cases by the simpler method of intravenous infusion of normal saline solution or by hypodermoclysis In case of circulatory collapse intravenous injection of whole blood or plasma may be life saving

The Sulfonamides

For a general discussion of the sulfonamide compounds the reader is referred to Chapter XXX-A by Maurice A Schnitzer in Oxford Medicine Vol IV

Bacteria Susceptible to the Sulfonamides — It is important to know when to use and when not to use sulfonamides They are most effective against the pneumococcus the meningococcus the gonococcus and the influenza bacillus They are potent in the commonest form that due to the beta hemolytic streptococcus but some cases prove resistant to sulfonamides and will yield to penicillin In staphylococcic septicemia the results have been disappointing and penicillin should be used from the start Bacteria less susceptible include the Friedlander bacillus *Bacillus welchii* and brucella However some good results have been reported in infection with these organisms

The colon bacillus is easily destroyed by the sulfonamides in localized infections of the urinary tract owing to the high concentrations, 50 to 200 mgm per 100 c c obtainable in the urine but it is impossible to kill these bacilli in the blood stream with any concentration of the drug which is safe However, by sterilizing the primary focus in the urinary tract further discharge of bacteria into the blood can be prevented so that sulfonamides are indicated here especially since penicillin is useless against the colon bacillus

Bacteria Not Influenced by the Sulfonamides — Anaerobic streptococci are not susceptible to the action of these drugs and their use is contraindicated in this form of septicemia The enterococcus *Streptococcus fecalis* is resistant to sulfonamides but septicemia due to this organism is very rare occurring chiefly as a terminal event in generalized peritonitis In suipestifer septicemia the sulfonamides have been ineffective and the same poor results may be expected in the case of any other member of the salmonella group Typhoid and paratyphoid bacilli are not susceptible

The Drug of Choice — In the treatment of septicemia sulfadiazine seems at the time of this writing to be the best of these compounds The newer drug sulfamerazine has the advantage of smaller dosage but it is difficult to maintain a constant level in the blood and this drug appears to be less reliable than sulfadiazine Sulfathiazole probably is equally as effective as sulfadiazine but it is

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Toxic reactions are much more frequent in cases receiving a second course of a sulfonamide especially if there has been a toxic response during the first course In that case it is well to give a test dose of 0 5 gm (gr $7\frac{1}{2}$) and if this is followed by a rash or increased fever the use of sulfonamides is contraindicated It is noteworthy however that, if a different form of the drug is used, toxic reactions may not take place

Nausea and vomiting frequent symptoms if sulfpyridine is given, are not encountered often in the case of sulfadiazine occurring with the latter in about 5 per cent It usually is possible to maintain an adequate blood level by continuing oral administration if not intravenous injections are indicated

Drug Fever — Fever usually sets in from the seventh to the tenth day from the beginning of treatment, sometimes earlier Often it is accompanied by a rash occasionally with arthralgia or even arthritis It subsides in two or three days if the drug is discontinued

Skin Rashes — A great variety of eruptions has been described The commonest is a maculopapular rash which sometimes resembles measles Macular eruptions are frequent less often there is a scarlatiniform eruption or urticaria, rarely thrombopenic purpura exfoliative dermatitis or a bullous eruption Erythema nodosum has been reported chiefly in connection with sulfathiazole Angioneurotic edema is a very rare manifestation

Occasionally there is involvement of the mucous membranes of the mouth or vagina in the form of red papules which may become eroded and covered with a white membrane A toxic conjunctivitis quite frequently is seen in patients receiving sulfathiazole The conjunctivae become intensely red and swollen but do not suppurate

Anemia — Two sorts of anemia may occur, acute hemolytic and secondary Acute hemolytic anemia occurs early in the course of treatment and is fairly frequent if sulfanilamide is used It has been reported though rarely with all the other sulfonamides It can be controlled by cessation of the drug and by transfusions of blood A mild secondary anemia may develop as a late reaction but is of little importance

Agranulocytosis — This fortunately is a rare occurrence, for usually it is fatal It may be met with after a prolonged course of any of the sulfonamides

Leucopenia and Leucocytosis — Leucopenia without reduction of the percentage of neutrophiles is fairly common and if progressive the drug should be stopped It is not a serious event Leucopenia before treatment has been started however is not a contraindication to the use of sulfonamides Leucocytosis attributable to the drug occasionally is present Eosinophilia is unusual

Renal Complications — These are among the most important and frequent toxic reactions They include hematuria oliguria and anuria Hematuria occurs in about 5 per cent and is not necessarily associated with crystalluria Most

often it is microscopic but gross hematuria sometimes with renal colic is met with in about 1 per cent Gross hematuria indicates withdrawal of the drug at least for a time

Oliguria and Anuria — These are due usually to blockage of the ureters with crystals and can be avoided by the use of alkali and a sufficient fluid intake If prompt cystoscopic treatment with lavage of the pelves with warm saline or preferably with soda bicarbonate is instituted the condition can be relieved

Much more serious though rare is a toxic nephrosis due to sulfonamides It is heralded by oliguria and leads to uremia and frequently, to a fatal termination It is an early manifestation usually in the first week of treatment It is evident that oliguria is a sign of serious import and indicates the prompt withdrawal of the drug

Hepatitis — This is a rare event in the case of sulfadiazine and sulfathiazole and has been reported chiefly after the use of sulfanilamide It takes the form of focal necrosis which very rarely may go on to acute yellow atrophy Clinically there is jaundice which may be difficult to distinguish from that due to septicemia Tests of liver function however show a moderate impairment in a fair proportion of cases but without other evidence of hepatic insufficiency

Nervous System — Cerebral symptoms occur in about 2 per cent They are distinguished from those due to the infection by the fact that they disappear when the drug is discontinued Dizziness and mental confusion are the commonest Yellow vision has been reported Peripheral neuritis is very rare

Treatment of Toxic Reactions — Toxic reactions unless they are mild call for withdrawal of the drug and the forcing of fluids to 3 000 c c or more If the infection still is active a switch to penicillin is indicated or one of the other sulfonamides such as sulfathiazole or sulfamerazine may be tried after an interval of a few days

Penicillin

For a general discussion of penicillin the reader is referred to Chapt XXX–B in Vol IV of Oxford Medicine

This remarkable drug was discovered by Fleming[19] in 1929 Using broth filtrates of *Penicillium notatum* he found an intense bacteriostatic action against the pyogenic cocci pneumococci gonococci meningococci and the bacillus of diphtheria It proved ineffective in the case of the gram negative bacilli and the enterococcus Fleming employed it in the isolation of the influenza bacillus and also as a local application in a few cases of infection of the skin

In 1940 Florey and his associates at Oxford [0] published the results of their extensive researches into the properties and methods of preparation of penicillin and reported the first therapeutic experiments with mice which were highly

successful In the following year the Oxford investigators[21] issued a second report including a clinical trial in staphylococcic and streptococcic infections They showed that penicillin is non toxic in therapeutic doses, and that its action is not inhibited by blood, pus or tissues, differing in this respect from the sulfon amides Favorable results were obtained in 5 cases

Since then numerous investigations have been made in England and America *production on a large scale has been achieved in the United States*, and the drug has been purified to a high degree though its exact chemical constitution has not been determined as yet Some idea of the enormous potency of penicillin may be gathered from the fact that in its purest form it inhibits the growth of staphylococcus aureus in a dilution of 1 in 25 million

Clinical investigation of penicillin on a large scale has been carried out in many hospitals in this country under the control of the Committee on Chemotherapeutic and other agents of the National Research Council As a result the indications for its use and the methods of administrations have been put on a firm basis though much work remains to be done

For further details concerning the history of penicillin, the reader is referred to articles by Fleming [2] and by Chain and Florey [3], to an editorial in the Journal of the American Medical Association[24] and to Vol IV, Chapt XXX-A of Oxford Medicine

Indications for the Use of Penicillin — The susceptible organisms encountered in septicemia in the approximate order of their sensitivity are as follows, gonococcus meningococcus, pneumococcus *Streptococcus hemolyticus*, anthrax bacillus *Staphylococcus aureus* *Staphylococcus albus* (most strains) *Clostridium welchii* (gas bacillus) *Clostridium septique* *Clostridium edematiens*, *Streptococcus viridans*, *Micrococcus tetragenus* and anaerobic streptococci It should be mentioned that there is a good deal of variation in the sensitivity of different strains of *Streptococcus viridans* and that the resistant strains of *Staphylococcus albus* are non pathogenic

Organisms not susceptible include the following colon bacillus, influenza bacillus Friedlander bacillus (*Klebsiella pneumoniae*) the typhoid group including *Salmonella suipestifer* and allied bacteria the dysentery group *Bacillus proteus* *Bacillus pyocyaneus* (*Pseudomonas aeruginosa*), enterococcus (*Streptococcus fecalis*) and brucella

It is interesting that the susceptible group includes almost all of the gram positive cocci also the gram negative *Neisseria* gonococcus and meningococcus while the gram negative bacilli without exception are resistant

Penicillin fastness has been demonstrated in the case of pneumococci, staphylococci and streptococci by growing the organisms in increasing concentrations of penicillin or by serial passages through mice which were treated with penicillin However, this is a rare occurrence in man and is, therefore, of little practical im

portance It is noteworthy that cocci which have become resistant to the sulfonamides are susceptible to penicillin and vice versa

The question of the combined use of penicillin and sulfonamides has been raised but at present there are no clinical data on the subject Rammelkamp and Keefer[25] and Bigger[26] have shown that in vitro the combination is more effective than either drug alone There would seem to be no objection to this method in exceptional cases

Comparison of Penicillin with the Sulfonamides — Penicillin is far superior to the sulfonamides in staphylococcic and gas bacillus infections It is definitely better in the case of the hemolytic streptococcus Anaerobic streptococci are resistant to sulfonamides and fairly susceptible to penicillin Penicillin is more active against the pneumococcus and is the drug of choice in septicemia due to this organism

The meningococcus is about equally sensitive to each of these compounds and either may be used In the case of the gonococcus however penicillin is the more effective and should be employed in all cases of gonococcal septicemia The sulfonamides are potent against the influenza bacillus and fairly so against Friedlander s bacillus both of which are resistant to penicillin

Methods of Administration — Penicillin is destroyed by the hydrochloric acid in gastric juice and if given by rectum it is inactivated by a ferment produced by the colon bacillus At the present time much work is being done on methods to protect penicillin from the action of hydrochloric acid but it has not reached a stage at which oral administration can be recommended so far as septicemia is concerned The subcutaneous route is not reliable and should not be employed There remain the intravenous and the intramuscular methods both of which have their advocates

If the intravenous route is chosen continuous injection is preferable to intermittent because the blood level is kept more constant and the need for frequent venipunctures is avoided It has the advantage of economy of material a smaller daily dose being required

Intramuscular injections can be given by nurses and therefore make less demands on the hospital staff The results obtained seem to be about as good as those with the intravenous route except in the case of bacterial endocarditis where a constant level of penicillin is necessary

Frequent administration is required because penicillin is excreted rapidly by the kidneys and the level falls quickly after intermittent injections The interval has been shortened from once every 4 hours in the early days of penicillin therapy to once every 3 hours or in desperate cases every 2 hours For continuous intravenous administration the dry powder is dissolved in sterile saline solution in the concentration of 25 to 50 units per c c In case a salt edema develops as happens occasionally 5 per cent dextrose in distilled water should be substituted

for the saline Continuous injection can be carried out also by the intramuscular route

Topical applications are advisable as a supplementary measure in wound infections and in empyema and meningitis Penicillin is not excreted into the normal cerebrospinal fluid but if meningitis is present considerable amounts pass through However it is safer not to rely on this but to make intrathecal as well as parenteral injections Penicillin is useful also when injected into suppurating joint cavities

Peck[7] has reported success in the treatment of carbuncles by local injections with a long needle of 5 to 10 c c in concentrations of 1,000 to 5,000 units per c c Lesions which resisted the parenteral administration of penicillin, responded rapidly when penicillin was injected into the carbuncle Surgical incisions also were employed as indicated

Dosage — While dosage has not been standardized there is a fair degree of agreement as to the amount to be used The dose varies with the bacterium concerned and with the severity of the infection For example the staphylococcus and non hemolytic streptococci require about double the amount needed in the case of more susceptible bacteria

With the intravenous drip a daily dose of 100 000 units usually is sufficient Enough should be given to inhibit the growth of the bacterium It is desirable to determine the sensitivity of the infecting organism at the start of treatment and also in selected cases the level of penicillin in the blood

If endocarditis is present the intravenous route should be chosen and much larger doses are needed 240 000 to 500 000 units in 24 hours or more up to 1 000 000 units being used customarily

For intramuscular injections 10 000 to 20 000 units every 3 hours is recommended The larger doses are advisable in infections due to staphylococci and non hemolytic streptococci The drug is dissolved in saline in a concentration of 5 000 units per c c In very severe infections an initial intravenous injection of 20 000 units is helpful and the interval between injections into the muscles may be reduced to two hours

For application to wounds penicillin is dissolved in normal saline solution in concentrations of 250 to 500 units per c c The dry powder is irritating and should not be used Intrathecal injections are given in the strength of 10,000 to 20 000 units in 10 c c of normal saline solution once or twice daily For empyema 20 000 units in 40 c c of normal saline solution is injected into the empyema cavity once daily or every two days after aspiration of the pus Most cases respond to this treatment but if there is no improvement within a week surgical drainage should be instituted The tendency to use larger doses by any route is increasing Dosage at present is in an unsatisfactory stage with the recognition that some forms of penicillin are much less effective therapeutically than others

Duration of Treatment — Treatment should be continued for 2 to 7 days after the temperature has become normal the longer period being advisable in staphylococcic and streptococcic infections In obstinate cases a more prolonged treatment may be necessary

Toxic Reactions — Owing to the extremely low toxicity of penicillin reactions are uncommon and never of a serious nature In the early days of penicillin therapy chills and fever were noted occasionally but these were due chiefly to impurities in the drug and now seldom are encountered Fever due to penicillin per se is said to occur occasionally but is difficult of recognition

Urticaria has been observed in about 1 per cent of cases It may appear during the course of treatment or several days after the drug has been discontinued a subsequent course of penicillin may not cause a recurrence of the rash Its causation is obscure but one instance of true allergy has been reported by Criep[8] The continued administration of penicillin seldom is contraindicated

Thrombosis at the site of injection is not uncommon in the cases of continuous venoclysis and calls for a shift to another vein Strictly speaking it is a mechanical rather than a toxic reaction for the vein does not become inflamed

Results to be Expected with Penicillin Therapy — Sterilization of the blood stream can be attained in close to 100 per cent Exceptions to be noted are the rare instances of penicillin resistant strains of staphylococci and some fulminating infections coming late to treatment In staphylococcic septicemia the mortality has been reduced from 80 per cent before the days of chemotherapy to 12 per cent in Herrell's[29] series and with early and intensive treatment a death rate of as low as 10 per cent may be predicted The fatal cases have been chiefly those with endocarditis Other deaths have occurred as a result of preexisting diseases of a lethal nature

In acute osteomyelitis surgical treatment usually is necessary but with penicillin it is possible to postpone operation to a favorable time and in a few cases a cure has been effected without the use of the knife In septicemia due to hemolytic streptococci the results have been highly encouraging but statistics are not available on a large enough scale to allow mortality figures to be stated Suffice it to say that penicillin has brought about a cure in cases which were resistant to the sulfonamides

Non hemolytic streptococci are more resistant, and the results achieved thus far have not been good but too few cases have been reported to admit of conclusions In 5 cases of septicemia due to anaerobic streptococci the mortality rate was 40 per cent to be compared with 90 per cent before the advent of chemotherapy

In pneumococcic septicemia owing to the frequency of endocarditis the mortality is rather high but with prolonged and intensive intravenous therapy encouraging results are being obtained Penicillin is very potent in meningococcic

septicemia but the results with the sulfonamides are so brilliant that it seldom is required In the case of the gonococcus, however penicillin is preferable, and cures have been reported in cases complicated with endocarditis

In infections with *Clostridium welchii* and kindred organisms penicillin is effective and is the drug of choice The best results are obtained if antitoxin also is given and surgical measures usually are necessary

Subacute bacterial endocarditis a disease which has proved resistant to sulfonamide therapy, recently has been shown to be amenable to treatment with penicillin The results obtained are discussed in the section on septic endocarditis

Serotherapy

The advent of the sulfonamides and of penicillin has rendered the use of sera superfluous in most instances Except in the case of diphtheria and scarlet fever sera now are never employed alone but only in conjunction with chemotherapy In streptococcic septicemia antitoxic serum may be useful in the rare cases where toxemia is overwhelming Staphylococcic antiserum likewise seldom is needed since the results with penicillin are so outstanding Julianelle[30] has reported a mortality rate of 50 per cent in 10 cases treated with antiserum alone, and serotherapy may be employed as an adjunct to penicillin in exceptional cases

The use of pneumococcus antiserum now seldom is necessary and may be restricted to fulminating infections The same remarks apply to meningococcic septicemia Septicemia due to the influenza bacillus often can be cured by the sulfonamides alone but a combination with serotherapy is considered by most to be a safer procedure

In infections caused by the gas bacillus group the best results are obtained if both serum and penicillin are employed In the case of anthrax antiserum has proved useful particularly in conjunction with sulfonamides but penicillin alone induced rapid recovery in 3 cases without bacteriemia reported by Murphy[31] Nothing has been published yet concerning the treatment of bacteriemic cases with penicillin but the results should be equally good

Immunotransfusion need be considered only in the case of septicemia complicating scarlet fever Blood obtained from convalescent donors is both antibacterial and antitoxic and its use has given brilliant results in the past It still could be useful in desperate cases

Surgical Treatment

The treatment of the primary focus often is necessary In the case of wound infections this goes without saying Furuncles can be let alone especially as the

offending boil usually has healed by the time septicemia sets in In sepsis arising from the tonsils tonsillectomy is contraindicated but peritonsillar abscesses should be incised and abscesses of the cervical lymph nodes should be opened and drained In acute osteomyelitis the infection of the blood stream can be controlled by penicillin and surgical measures can be postponed until a more favorable time

Ligation of veins leading from the primary focus seldom is indicated If there is a thrombosed vein easily accessible as in the arm or leg it may be advisable to ligate it in special cases However ligation of an open ductus arteriosus in cases complicated with *Streptococcus viridans* septicemia has produced brilliant results

Metastatic abscesses should be incised and drained if they are accessible This is very important for they may serve as secondary foci of infection of the blood stream In the case of otogenous septicemia surgical treatment is indicated but the results have been greatly improved by the use of sulfonamides and of penicillin The mortality is much lower in those cases in which an early exploration of the lateral sinus is done

II

Special Forms of Septicemia

In this section a description of the different forms of septicemia according to the organism involved will be given This involves some repetition but is necessary if a comprehensive idea of the subject is to be gained

Septicemia due to Streptococcus

This is the commonest form being met with in at least 60 per cent of the cases The streptococcus has no favorite portal of entry invading the blood with almost equal frequency from the skin from the throat and from the puerperal uterus Less frequently the primary focus is in the urinary or alimentary tract the ears or the nasal sinuses Secondary septicemias occur fairly often in scarlet fever less often in diphtheria and other acute infectious diseases

For purposes of classification here it appears better to avoid the usual Bergey Manual[27] classification and to divide the group as follows (1) streptococcus *hemolyticus* (2) *streptococcus viridans* (3) *anhemolytic streptococci* and (4) anaerobic streptococci These constitute the most important varieties It is obvious that there are various strains in each of these groups as evidenced by differences in biological reactions i e cultural differences toxin formation etc Each strain may be modified by its environment and as a result show variation in

septicemia but the results with the sulfonamides are so brilliant that it seldom is required In the case of the gonococcus however penicillin is preferable, and cures have been reported in cases complicated with endocarditis

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Serotherapy

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Immunotransfusion need be considered only in the case of septicemia complicating scarlet fever. Blood obtained from convalescent donors is both antibacterial and antitoxic and its use has given brilliant results in the past. It still could be useful in desperate cases.

Surgical Treatment

The treatment of the primary focus often is necessary. In the case of wound infections this goes without saying. Furuncles can be let alone, especially as the

In septic sore throat septicemia is fairly common and is present in most of the fatal cases This disease which is due to a special group of hemolytic streptococci is fully described elsewhere in this system (see Vol V Chapt I) It occurs in milk borne epidemics the contamination of the milk probably arising from a streptococcic infection of the udder Generalized acute peritonitis frequently is associated with septicemia due to this organism and then apparently is of hematogenous origin

Puerperal and otogenous streptococcic septicemia are described under special headings farther on

Occasionally septicemia originates from a streptococcic pneumonia In such cases it is probable that thrombophlebitis of a small pulmonary vein constitutes the septic focus Septicemia was very uncommon in the course of the streptococcic empyema which was so frequent a complication of influenza and measles during the first World War indeed doubt has been expressed that the blood stream is ever infected directly from the pleura or the peritoneum rather than from an accompanying thrombophlebitis

The urinary tract occasionally is the portal of entry in streptococcic septicemia Invasion of the blood stream from the alimentary tract sometimes takes place in the case of ulcerated cancers of the esophagus and stomach and in infants dying of acute ileocolitis Rarely it occurs in the acute streptococcic enteritis of adults Perforative appendicitis with generalized peritonitis rarely is complicated with streptococcic septicemia

The frequency of streptococcic infection in scarlet fever has been mentioned already Less often septicemia usually due to the streptococcus occurs in diphtheria In smallpox secondary infection with the streptococcus is the rule and most of the fatal cases show positive blood cultures In typhoid fever and dysentery streptococci may penetrate into the blood from the ulcers

The clinical picture of streptococcic septicemia does not differ essentially from that due to other organisms The frequency of metastases is much less than in staphylococcic infections The course usually is acute very seldom chronic The type of fever has been described already There is a very marked tendency to arthritis more so than in any other infection except rheumatic fever Lenhartz observed purulent arthritis in one half of the fatal cases Metastases to the lungs come next in frequency being noted especially in the puerperal and otogenous forms Endocarditis is not uncommon Erythemas and petechiae often are noted pustular eruptions rarely Occasionally large bullae with hemorrhagic contents appear In a recent personal case there were extensive patches of infiltrated reddened skin closely resembling erysipelas

Prognosis — The outlook has improved enormously since the advent of chemotherapy The mortality previously from 60 to 80 per cent now should be in the neighborhood of 10 to 20 per cent

colony formation At the moment and certainly as far as this article is concerned, it is not practical to consider the mucoid types of hemolytic streptococci as any thing other than variant hemolytic streptococci

Septicemia Due to the Streptococcus Hemolyticus

Septicemia due to this organism is the commonest form to be encountered in practice The portal of entry may be either the skin or the mucous membranes Infection from the skin arises from infected wounds phlegmons, suppurative tenosynovitis or ulcers and these cases come to the surgeon rather than to the internist Erysipelas may be complicated with septicemia and hemolytic streptococci can be cultivated from the blood in most of the fatal cases of this disease

Septicemia arising from the throat occurs oftenest in scarlet fever, in which it is one of the chief causes of mortality Uusually the starting point is a necrotizing tonsillitis This is accompanied with a marked swelling of the cervical lymph nodes and often a sero sanguineous nasal discharge having a peculiar, disagreeable odor It should be noted however that streptococci sometimes are to be found in the blood in less severe cases of scarlet fever so that a positive blood culture though always a serious sign does not necessarily involve a bad prognosis

Septicemia arising from an ordinary acute follicular tonsillitis is sufficiently common to warrant a brief description though rare in proportion to the great frequency of this malady The pathway of infection usually is by way of the veins either directly with thrombosis of the retrotonsillar vein as described by E Fraenkel[33] or indirectly with extension of a phlegmonous process in the neck into the internal jugular or facial veins occasionally it is by way of the lymphatics, starting from an abscessed lymph node

Most cases of post anginal septicemia follow a peritonsillar abscess in others a simple tonsillitis has preceded the throat infection may have been mild and apparently healed by the time that septicemia sets in Usually the septic focus is on the same side as the more diseased tonsil but it may be on the opposite side and in not a few instances the offending tonsil appears normal until serial sec tions disclose a small abscess within it Septicemia may start at any time within a period of three days to eight weeks after the initial sore throat The onset is sudden with high fever and marked symptoms of toxemia usually there is a chill Examination shows the signs of tonsillitis or if these have disappeared tenderness at the angle of the jaw is almost always there to reveal the source of the trouble The thrombosed veins usually are not palpable unless the internal jugular is extensively involved The diagnosis should be suspected if a chill occurs after the third day in a case of tonsillitis although an initial chill is not uncommon in uncomplicated acute tonsillitis

The *treatment* is symptomatic for the enterococcus is not susceptible to sulfonamides nor to penicillin However it would be wise to test the culture obtained from the patient as to its sensitivity to penicillin for it is possible that occasional strains may be susceptible

Septicemia Due to Anaerobic Streptococci

Septicemia caused by anaerobic streptococci has been reported frequently in Germany seldom in America and Great Britain The cause for this disparity probably lies in the infrequent use of anaerobic culture methods in the two latter countries The clinical picture was described first in 1910 by Schottmuller[39] of Hamburg who found this organism a common cause of death following criminal abortion Later investigations have come chiefly from Bingold[40] also of the Hamburg school from Colebrook and Hare[41] and White[4] in England and from Schwartz and Dieckman[43] and Fisher and Abernethy[44] in America

A number of different strains of anaerobic streptococci have been described differing in their fermentation reactions and hemolytic activity but almost all producing gas and a foul odor The *Streptococcus putrificus* (Schottmuller) is the type encountered most often in practice It is a constant inhabitant of the vagina of healthy women and is found in various local infections where anaerobic conditions are present such as endometritis following abortion or childbirth in plugs in the tonsillar crypts in pyorrheal pockets in some cases of mastoiditis and rarely in pyelitis In pulmonary gangrene and putrid empyema it is present almost constantly It has been found not infrequently in acute appendicitis In other parts of the body it is so rarely infective that the finding of anaerobic streptococci in the blood stream points almost with certainty to a primary septic focus in the female genital tract the ears, the throat the lungs or the intestine (Schottmüller and Bingold[12])

The chief importance of the anaerobic streptococcus as a cause of septicemia lies in connection with septic abortions and puerperal fever in which it occurs equally as often as the ordinary aerobic *Streptococcus hemolyticus*[9] This statement seems surprising but it is sustained by the results of all recent investigations in which both aerobic and anaerobic methods have been employed It applies both to local and generalized infections of the genital tract during pregnancy and the puerperium for Harris and Brown[45] found this proportion to obtain in 113 cases of streptococcic puerperal infection from the Johns Hopkins Clinic in none of which septicemia was present

The distinguishing feature about infections with the anaerobic streptococcus is the ability of this organism to cause gangrenous processes protein being dissolved with the production of a putrid odor both in the living body and in the test tube This is apparent both in the primary focus and in the metastases In the

Treatment — Penicillin has proved to be so much superior to the sulfonamides against the hemolytic streptococci that this drug should be used from the start in all but mild cases

Septicemia Due to Streptococcus Viridans

The *Streptococcus viridans* is present frequently in inflammations of the upper respiratory tract and about the teeth less often in those of the intestines and female genital tract It has been found by Schottmuller[34] in pure culture in the pus of meningitis lung abscess and pericarditis and in the blood stream in pyle phlebitis In the case of subacute bacterial endocarditis it is the causative organ ism in about 95 per cent Apart from this condition however it is rarely a cause of septicemia A temporary bacteremia on the other hand is encountered oc casionally in acute inflammations of the upper respiratory tract and in septic abortions Septicemia when it does arise usually runs a favorable course in the absence of endocarditis owing to the low virulence of this organism The portal of entry usually is the throat less often the intestines rarely the puerperal uterus and here only in association with other bacteria Exceptionally ulcerative aortitis without endocarditis is found as the septic focus in cases running the clinical course of subacute bacterial endocarditis Siegmund[35] noted this localization in three instances among 165 autopsies of cases of chronic viridans septicemia the remainder being associated with endocarditis In the case of Hamman and Rienhoff[36] an arterio venous aneurysm was the site of the septic focus and re covery followed excision of the aneurysm

Septicemia Due to Anhemolytic Streptococci

Anhemolytic streptococci are found chiefly in the intestine and constitute a large group containing many varieties judging from their varying reactions in regard to the fermentation of carbohydrates They are constantly present in normal stools hence their name *Streptococcus fecalis* or enterococcus Their pathogenicity for man certainly is very low and many authorities regard them as merely secondary invaders when they are met with in localized inflammatory processes Rantz and Kirby[37] reported the presence of enterococci in post mortem cultures of the heart s blood in 4 of 8 cases of perforative peritonitis twice in pure culture no blood cultures were taken during life They described also a case of brain abscess following mastoiditis with septicemia due to the enterococcus Moreover they isolated enterococci as the causative agent in 3 of 16 cases of subacute bacterial endocarditis Moran[38] had a similar experience These findings suggest that some cases of this disease, which are resistant to penicillin are due to one of the enterococcus group

ably are derived from the skin In puerperal septicemia the staphylococcus plays an important part being noted in 2 per cent of Schottmuller and Bingold's[12] large series Occasionally the tonsils constitute the primary focus In osteomyelitis which usually is a staphylococcic disease the original infection of the bone is by way of the blood stream but the bacteria proliferate in the bone focus and constitute in their turn a source of blood infection A considerable proportion of the cases of staphylococcus septicemia in surgical clinics is associated with osteomyelitis

Infection from the skin takes place usually from paronychiae superficial infections furuncles and carbuncles rarely from impetigo eczema or vaccination *The vast majority of cases of staphylococcic septicemia is due to the staphylococcus aureus* the remainder to the albus

Staphylococcic septicemia is characterized especially by the frequency of metastatic abscesses which occur in no less than 95 per cent although by no means always demonstrable in life The kidneys are the most frequent site showing usually multiple miliary abscesses The lungs myocardium and brain often are involved The more chronic cases often show abscesses in the muscles and subcutaneous tissues Occasionally a perinephric abscess constitutes the only metastasis Acute endocarditis is more frequent than in streptococcic septicemia being noted by Jochmann[14] in 9 of 23 cases

The course usually is acute with high continuous or remittent fever The *average duration of the fatal cases is about two weeks while those that recover* often have a protracted convalescence owing to the occurrence of multiple abscesses in the muscles and subcutaneous tissues Skin rashes are common usually either pustular or petechial The pustular rash is strictly speaking not pustular but begins as pin head to pea sized vesicles with red areolae the contents quickly become purulent It is quite characteristic and of great diagnostic value

The clinical picture is varied depending upon the situation of the metastases Pericarditis hemiplegia or convulsions as a result of cerebral lesions suppurative parotitis or epididymitis are among the striking features The abscesses in the kidney usually give rise to no symptoms and their only sign is the appearance of staphylococci in the urine

Osteomyelitis is so frequent a cause of staphylococcic septicemia and its early recognition is so important from a therapeutic point of view that a brief description of it seems advisable Primary osteomyelitis is almost always a staphylococcal infection Streptococci pneumococci and typhoid bacilli occasionally cause bone lesions but this occurs late in the disease and the involvement of the bone marrow usually is not extensive the main signs being those of periostitis

Infection takes place by way of the blood stream usually from the skin The focus in the bone marrow is most often in the metaphysis that part of the shaft next to the epiphysis rarely in the epiphysis The femur and the tibia are in

case of puerperal infections, the lochia have a putrid odor, the placental remains and the endometrium are changed to a foul black semifluid material, the thrombi in the pelvic veins become discolored and softened the metastases become gangrenous The path of infection is by way of the veins Metastases to the lungs occur in almost every case but the pulmonary filter seldom is passed, and metastases to other parts of the body are unusual Endocarditis, arthritis and meningitis are noted infrequently Small abscesses in the spleen occurred in 5 per cent of Bingold's[10] cases If however the primary focus is in the lung, one would expect abscesses in the distribution of the greater circulation, and this actually happened in the case of Fisher and Abernethy[41] in which pulmonary gangrene with putrid empyema was followed by subcutaneous gas containing abscesses and metastatic suppuration of a clavicle and knee joint

The clinical course usually is protracted lasting a month or longer Chills are frequent, and the fever is of the familiar septic type with deep remissions and intermissions Locally the thrombophlebitic process may be revealed by a palpable tender cord in the broad ligament sometimes accompanied by extension to the neighboring tissues and abscess formation in the pelvis

The pulmonary metastases which occur in almost every case go on to the formation of small putrid abscesses or gangrene usually multiple they may be single and large in which case they resemble closely pulmonary gangrene of non embolic origin Although cough and pain in the chest may be absent physical signs of pulmonary involvement usually are present, there is localized dulness with diminished breath sounds and râles more rarely the respiration is amphoric owing to extensive cavitation or bronchial if the neighboring parts of the lung become consolidated The sputum is foul and contains anaerobic streptococci If the patient recovers from the septicemia the gangrenous process in the lung may heal as in the case reported by Bingold[16] Putrid empyema is not uncommon

The prognosis now is fairly good Anaerobic streptococci are resistant to the sulfonamides but are susceptible to the action of penicillin The mortality, formerly 90 per cent should be reduced considerably by penicillin therapy, it is too soon to give exact figures but there were 3 recoveries out of 5 cases mentioned in the committee report of Keefer and others[47]

Septicemia Due to Staphylococcus

The staphylococcus ranks next to the streptococcus as a cause of septicemia, on combining the statistics of Warren and Herrick[10] Bertelsmann[11] and Lenhartz[9] we find 156 cases due to the streptococcus and 75 to the staphylococcus In contrast to the streptococcus the portal of entry usually is the skin Next in frequency comes the urethra a number of cases being reported after the dilating of urethral strictures or the passage of catheters In this case also the bacteria prob

stances it occurs in connection with lobar pneumonia in others it is secondary to infection of the ears tonsils meninges bile passages or uterus

The onset usually is towards the end of the first week in pneumonia or after a short afebrile period following the crisis The temperature chart often shows deep remissions or intermissions in contrast to the continuous fever of the preceding pneumonia Chills are not uncommon

Acute endocarditis usually of the ulcerative variety is frequent The course of the disease is short from 1 to 3 weeks Lenhartz has reported one case lasting several months

Two features stand out as peculiar to pneumococcus sepsis (1) the frequency of meningitis as a terminal event noted by Jochmann[48] in 10 of 18 cases (2) the frequency with which the aortic valves are affected A similar preference for the aortic valves is found only in gonococcal septicemia

In spite of the fact that as E Fraenkel[51] has shown pneumococci can be cultivated from the bone marrow in all fatal cases of lobar pneumonia osteomyelitis is rare Suppurative pericarditis is not uncommon infection taking place either through the blood stream or by extension from the pleura Suppurative peritonitis may occur usually with diarrhea Arthritis is not so common as in streptococcic infections when it occurs usually it is purulent and in one half the cases it is confined to a single joint According to Cave[5] the knee shoulder wrist elbow and sternoclavicular articulation are the joints involved most frequently and in the order named

Rarely metastatic abscesses have been reported in the parotid and thyroid glands and in the muscles Skin eruptions are very unusual Infarcts in the viscera may occur in cases with endocarditis and do not necessarily suppurate Panophthalmitis has been reported

The *diagnosis* is probable if there is fever following pneumonia with signs of cardiac involvement or of metastases It is rendered certain by the results of blood culture The senior author remembers a case seen in his intern days in which the first indication of septicemia was severe pain in the right side of the abdomen with spasm and an operation for a supposed appendicitis was performed The appendix was normal and later an aortic regurgitant murmur appeared the autopsy revealed large vegetations on the aortic valve and massive infarction of the right kidney

The prognosis formerly very bad has improved since the introduction of chemotherapy Now many of these patients can be saved although owing to the frequency of endocarditis the outlook is not so good as in staphylococcic septicemia However a fair percentage of recoveries from endocarditis about 30 per cent is being obtained with intensive intravenous penicillin therapy Penicillin is superior to the sulfonamides in pneumococcic septicemia and should be employed from the start

volved most often The process is confined usually to one bone but often several are involved Necrosis of the bone marrow is followed soon by suppuration The process next extends to the cortex and thence to the periosteum with the formation of a subperiosteal abscess Finally, the suppuration extends to the soft tissues or through the epiphysis into the neighboring joint Later on the necrotic center is separated as a sequestrum, while new bone is laid down outside it from the periosteum

Primary osteomyelitis is a disease of youth, 59 per cent according to Lexer[49] falling in the second decade with few cases after the age of 25 It occurs in the period of growing bone which offers a suitable nidus on account of its vascularity and cellular activity Predisposing causes are cold, fatigue, trauma and recent attacks of the exanthemata

The onset is acute with intense localized pain in the bone usually near the epiphysis The pain is aggravated by pressure Nichols[50] called attention to a valuable diagnostic sign continued gentle pressure made over the bone at a distance from the seat of the greatest pain at first produces no pain, but in a little while the pain becomes intense In some cases pain is only moderate in the early days Soon a localized inflammatory swelling of the soft parts appears and effusion may take place into the neighboring joint either serous or purulent The fever and pulse usually are high and the signs of toxemia very evident A marked leucocytosis is the rule from 20 000 to 40 000 Blood cultures according to Bertelsmann[11] are always positive in the acute stage but soon become negative in the cases that recover

The *diagnosis* is easy in most cases if the disease is thought of at all The mistaken diagnosis of rheumatism often is made but with a little experience this should not happen The toxemia is much greater than in rheumatic fever and the local findings quite different

The *prognosis* in staphylococcic septicemia now is very good With penicillin therapy a mortality of about 1[illegible] per cent may be expected as against 70 per cent formerly The fatalities are due chiefly to endocarditis, but about 25 per cent of those with this complication may be saved by penicillin Formerly all of them died

Treatment should be with penicillin in full doses The sulfonamides are much inferior to penicillin in the case of the staphylococcus On account of a tendency to relapse it is best to continue the injections for a week or 10 days after the temperature has become normal

Septicemia Due to Pneumococcus

Bacteriemia during acute lobar pneumonia is a frequent finding True septicemia due to the pneumococcus is encountered occasionally In most in

stances it occurs in connection with lobar pneumonia; in others it is secondary to infection of the ears, tonsils, meninges, bile passages or uterus.

The onset usually is towards the end of the first week in pneumonia or after a short afebrile period following the crisis. The temperature chart often shows deep remissions or intermissions in contrast to the continuous fever of the preceding pneumonia. Chills are not uncommon.

Acute endocarditis, usually of the ulcerative variety, is frequent. The course of the disease is short, from 1 to 3 weeks. Lenhartz has reported one case lasting several months.

Two features stand out as peculiar to pneumococcus sepsis: (1) the frequency of meningitis as a terminal event, noted by Jochmann[48] in 10 of 18 cases; (2) the frequency with which the aortic valves are affected. A similar preference for the aortic valves is found only in gonococcal septicemia.

In spite of the fact that, as E. Fraenkel[51] has shown, pneumococci can be cultivated from the bone marrow in all fatal cases of lobar pneumonia, osteomyelitis is rare. Suppurative pericarditis is not uncommon, infection taking place either through the blood stream or by extension from the pleura. Suppurative peritonitis may occur, usually with diarrhea. Arthritis is not so common as in streptococcic infections; when it occurs usually it is purulent, and in one half the cases it is confined to a single joint. According to Cave[5] the knee, shoulder, wrist, elbow and sternoclavicular articulation are the joints involved most frequently and in the order named.

Rarely metastatic abscesses have been reported in the parotid and thyroid glands and in the muscles. Skin eruptions are very unusual. Infarcts in the viscera may occur in cases with endocarditis and do not necessarily suppurate. Panophthalmitis has been reported.

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Septicemias Due to Gonococcus and to Meningococcus

For these the reader is referred to the chapters on gonococcal infections (see Vol V, Chapt III) and on epidemic meningitis (see Vol V, Chapt IV)

Septicemia Due to Colon Bacillus

A constant inhabitant of the intestine in health the colon bacillus at times becomes pathogenic and is a fairly frequent cause of local inflammations both with and without suppuration It is the commonest cause of pyelitis and is often found in appendicitis and diseases of the bile passages In spite of the ubiquity of the colon bacillus septicemia due to this organism is far from common The bacillus shows little tendency to invade the blood stream from local lesions and if it does apparently is quickly killed in the blood For this reason it is questionable whether some of the reported cases of pyelitis etc with positive blood culture should not be regarded merely as bacteriemia In other instances, however a true septicemia has arisen with purulent metastases and as in the case of Hitschmann and Michel[3] and a personal one of the senior author with the presence of acute ulcerative endocarditis with colon bacilli in the vegetations

The portal of entry usually is the urinary tract much less frequently the female genitalia the intestines or the bile passages Infection from the urinary tract takes place most often from pyelitis or from the urethra especially after instrumentation as in dilating a stricture The colon bacillus has been isolated from the blood during catheter fever either alone or with the staphylococcus or the streptococcus Colon septicemia starting from the bile passages is rare and occurs chiefly in inveterate cases of chronic cholecystitis or cholangitis sometimes associated with stone in the common duct It has been reported also in acute cholecystitis

In the cases of intestinal origin the appendix most often is at fault The invasion of the blood stream follows not directly but by means of thrombosis of the mesenteric vein and the portal vein with purulent softening and abscesses of the liver In other similar cases however the infection has remained limited to the liver and no bacteriemia has resulted In a few instances such as the third case of Wiens[54] an acute gastroenteritis has been the starting point in other instances dysentery cholera tuberculous ulcers or carcinoma of the colon Ilfeld[55] describes two fulminating cases with hyperpyrexia immediately following operation on the stomach for ulcer

Although the colon bacillus is often to be found usually associated with other bacteria, in the uterine discharge in acute endometritis it is rarely the cause of puerperal sepsis Thus in Schottmuller and Bingold s[1] large series of fatal cases it was not present once in pure culture though in 7 cases it was recovered from the

blood stream in association with other pathogens Jacob[56] reported 11 cases of which 3 were personal Two were mixed infections with streptococci Usually the thrombophlebitic form with metastatic abscesses was present

The clinical picture of septicemia due to the colon bacillus often is dominated by the local inflammatory process In other instances it is that of septicemia with a strong tendency to the intermittent type of fever accompanied usually with chills Icterus is fairly common in the absence of infection of the liver or of the biliary system It is similar in origin to that seen in septicemia due to other organisms It is doubtful if the colon bacillus ever causes brown jaundice with hemoglobinuria such as is so characteristic of puerperal infections with the gas bacillus in Felty s[5] case both the gas bacillus and the colon bacillus were present in the blood stream and in that of Blackader and Gillies[58] typical in all respects of infection with *Cl welchii* anaerobic cultures were not taken Leucocytosis is absent or slight in the uncomplicated cases excepting just after a chill considerable in those with metastatic abscesses and very marked in pylephlebitis

Metastases occur in about 20 per cent most commonly in the lungs and kidneys Endocarditis either of the verrucous or the vegetative type is an occasional complication Herpes is common and may be extremely profuse in which case it has diagnostic importance (Schottmuller and Bingold[1] and personal observation) Other skin eruptions are unusual The diagnosis is probable if repeated chills and fever occur in the course of a localized infection with the colon bacillus and is confirmed by the results of blood cultures

The *prognosis* is better than in most other forms of septicemia the mortality in a series reported by Felty[57] being only 32 per cent The colon bacillus is not susceptible to penicillin and is not destroyed by concentrations of sulfonamides obtainable in the blood

In *treatment* the sulfonamides should be used in full doses in order to sterilize the primary focu if possible (For further discussion see Vol IV Chapt XXII)

SEPTICEMIA DUE TO FRIEDLANDER S BACILLUS (*KLEBSIELLA PNEUMONIAE*)

Friedlander s bacillus is characterized by capsule production and by a slimy growth in cultures It is gram negative It is closely related to *B lactis aerogenes* and sometimes cannot be distinguished from it by fermentation tests Julianelle[59] has shown by biological methods especially by means of specific antisera that Friedlander s bacillus may be divided into several groups viz types A B and C and a miscellaneous group X composed of strains that do not react with one another or with members of the 3 types Most of the strains isolated from man belong to the first two types in the proportion of 70 per cent type A and 30 per cent type B The latter type has been shown to be closely related immuno-

logically to type II pneumococcus and type II antipneumococcus serum has proved effective against experimental infection of mice with Friedlander's bacillus type B. The Friedlander bacillus occurs in the nose and throat of about 5 per cent of healthy persons. It may cause local inflammations in any part of the body with a marked tendency to suppuration so that Étienne has called it a bacillus "a tout faire". It is found in connection with inflammation of the eyes, the nasal passages and the ear, in meningitis, peritonitis, hepatic abscess, salpingitis, cystitis, pyelitis, gastroenteritis and cholecystitis. It is the cause of a small proportion of lobar and bronchopneumonia, 1 to 4 per cent. Baehr, Swartzman and Greenspan[60] in a large series showed that contrary to the general belief most of the infections arise not from the respiratory tract but from the abdomen or the urinary tract. Only 16 of 198 cases involved the respiratory tract, the remainder were about equally divided between appendiceal abscesses, infections of the biliary passages and of the urinary tract.

Septicemia due to the Friedlander bacillus is rare. For the literature the reader is referred to articles by Meyer and Amtman[61] and by McCall and Freeman[62].

The portal of entry most frequently is the intestine, the biliary or the genito-urinary tract. Less often the infection starts from the middle ear, tonsils, uterus, lungs or the umbilicus in the new born.

Males are affected much more often than females, and most of the cases occur in those past middle age. A rather high proportion has been associated with diabetes.

The course is acute with high fever, either continuous or more frequently intermittent, with chills and sweats. A fulminating case was reported by Blumer and Laird[63] with death in 36 hours. Vomiting and diarrhea often are prominent symptoms, which may be correlated with the marked engorgement of the intestines found at autopsy. Positive blood cultures usually may be obtained, but the bacilli are not agglutinated by the patient's serum. Occasionally rashes are noted: maculopapular, scarlatiniform or petechial. Jaundice may be present. Ulcerative endocarditis has been reported in a few cases. Hepatic abscess is a rather common occurrence: in 30 cases of liver abscess described by Kinney and Ginsberg[64] Friedlander's bacillus was the cause in 7, 23 per cent. The clinical picture may be dominated by a local process, as in the case of Wersig[65] in which operation on the kidney was performed for metastatic abscesses. Jenssen[66] reported an instance of a metastatic abscess perforating into the peritoneal cavity. Rolly[67] observed cases after abortion and in the puerperium. Lereboullet and Denoyelle[68] reported 2 unusual cases in children ending in recovery, in which the course simulated typhoid fever, even to the presence of rose spots.

At autopsy metastatic abscesses in the lungs, liver and kidneys have been found. The spleen is enlarged. The intestine often shows a high degree of con-

gestion The mortality is high in the neighborhood of 85 per cent Probably it will be reduced by treatment with the sulfonamides but too few cases have been reported to allow figures to be given

The sulfonamides are the most effective drugs at the present time The experimental work of Feinstone and others[69] and of Sesler and Schmidt[70] has shown that in mice sulfadiazine is quite potent much more so than sulfathiazole or sulfapyridine while sulfanilamide was ineffective A few instances of recovery with sulfonamides have been reported In Turnbull s case[71] sulfadiazine caused prompt improvement after sulfathiazole had failed Penicillin is powerless against Friedlander s bacillus as in the case of other gram negative bacilli

In the case of type B infections antipneumococcus serum type II may be employed in conjunction with sulfadiazine as practised by Perlman and Bullowa[72] in the treatment of Friedlander pneumonia It is not effective in the case of type A

Septicemia Due to Bacillus Pyocyaneus (*Pseudomonas Aeruginosa*)

The bacillus pyocyaneus often called the bacillus of green pus at first was regarded as a harmless saprophyte Charrin[3] however in 1889 showed it to be pathogenic for animals and more recently it has been found to be the cause in man not only of local inflammations but also of septicemia It is often present in the dung of animals especially swine but it is not a common inhabitant of the human intestine either in health or disease It is found sometimes on the skin and in the sweat and the saliva

Locally it is met with most often as a secondary invader in infected wounds and is recognized readily by the greenish color and the peculiar odor of the pus It is found quite frequently in the discharge in chronic otitis media In the eyes it may cause conjunctivitis inflammation of the eyelids with necrosis and ulcers of the cornea Very rarely it has been isolated in cases of membranous tonsillitis and esophagitis Occasionally it is found in infections of the bladder and of the pelvis of the kidney usually associated with other bacteria and may impart a greenish color to the urine It has been reported in the stools in ward epidemics of enteritis in children Calmette[74] found it in the stools in the diarrhea of Cochin China and Lartigau[5] in the stools in a small epidemic of dysentery and in the drinking water

In spite of its common occurrence locally it is rarely a cause of general infection as shown by the fact that Simmonds did not find it once in cultures of the heart s blood in 1 200 autopsies Nevertheless owing to the fact that most of the cases are reported there is quite a large literature on the subject of pyocyaneous septicemia

At autopsy the striking feature is the frequency of necrotic foci in the mouth

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At autopsy the striking feature is the frequency of necrotic foci in the mouth

throat, stomach, intestines, trachea, lungs, kidneys and skin. In the mucous membranes these lesions appear as shallow ulcers with a hemorrhagic areola; in the lungs as hemorrhagic bronchopneumonia; in the kidneys they resemble small infarcts; and in the skin there are infiltrated wheals, blebs and punched out ulcers. The tendency to capillary hemorrhage in these lesions is very pronounced. Fraenkel[6] has shown that in all these situations the necrosis is the result of infection of the wall of the arteriole with pyocyaneus bacilli, which are present in countless numbers in the adventitia. This finding is so constant and characteristic that it is of itself diagnostic of pyocyaneus infection according to Fraenkel. Suppuration in these necrotic lesions is conspicuous by its absence, and metastatic abscesses are met with rarely in the absence of mixed infection. Meningitis is rare and usually is of otitic origin. Endocarditis with cultivation of the bacilli from the valves has been reported in infants by Blum[77], Benfey[78] and Hess[79] and in an adult by Kolly[80].

In the majority of cases with positive blood cultures the organism has been found pure, less often associated with other bacteria. While most of the cases have occurred in infants and young children, a considerable number has been in adults. Wassermann[81] has reported an epidemic resulting from infection of the umbilicus in the new born.

As a rule pyocyaneus septicemia affects people who are debilitated by previous disease. The portal of entry usually is the intestine, the skin or the middle ear or the urinary tract. The course is acute, rarely chronic. The onset often is violent with high fever, vomiting and diarrhea. The fever is apt to be continuous or remittent, the duration of the disease seldom is more than two weeks. The leucocytes are normal in number or decreased. Epstein and Grossman[82] have recorded a case in which there was a terminal granulocytopenia with reduction of the platelets to a very low figure. Diarrhea with blood streaked stools is common, and sigmoidoscopy may reveal erosions of the mucous membranes as in the case of Baumeister[83]. Superficial grey green ulcers of the hard palate, tonsils or nasopharynx may be visible and may show pyocyaneus bacilli on culture. The spleen often is enlarged.

A characteristic rash is present in more than one half of the cases and is of great diagnostic value. The lesions usually are multiple and appear at first as raised, round, infiltrated areas of a reddish brown color, often with a hemorrhagic halo. Very soon a bleb forms at the center of the spot with turbid or bloody contents. The bleb ruptures and necrosis takes place with the formation of rather deep, punched out, circular ulcers, one to several centimeters in diameter; blackish crusts may or may not be present. Favorite sites are the axillæ and the trunk from the umbilicus down and the upper part of the thighs, especially the perineal region. The skin lesion is known to dermatologists as echthyma gangrenosum and is distinguished from the ordinary echthyma vulgare by the absence

of suppuration in the former Cultures from the blebs and from the base of the ulcers show pyocyaneus bacilli usually in a state of purity Petechiæ may occur either alone or associated with the echthymatous lesions

An interesting chronic case has been described by de la Camp[84] The onset was characterized by headache with obstruction of the nose bloody nasal discharge and fever After two months the fever was accompanied with daily chills and a profuse purpuric rash appeared For a period of 10 months there were recurring ulcers of the feet and legs starting as red areas which turned to blebs and discharged a bloody fluid When seen by the author there were two ulcerated nodules on the legs resembling gummata One was excised and injected into a guinea pig and a pure culture of pyocyaneus was obtained The duration was one year Death followed an operation for mastoiditis due to pyocyaneus This organism was grown also from the heart s blood at autopsy

Freeman[85] also described a chronic case lasting 11 months which probably started from the gall bladder The course was characterized by a daily intermittent fever with chills and by the appearance of maculopapular and urticarial eruptions followed by a rash like erythema nodosum which recurred at intervals for 9 months There was also a multiple neuritis Charrin observed paralysis of the hind legs in his infected animals Cure resulted after drainage of the gall bladder the contents of which showed pyocyaneus in pure culture Blood culture was negative

The complications are those usual in septicemia Endocarditis is very rare Moragues and Anderson[86] reported a case and reviewed the literature of 6 cases Meningitis occasionally occurs as in the case of Slutsky and Matlin[87] An interesting series of 6 cases following lumbar puncture and due to the use of a mercury manometer was reported by Wise and Musser[88] The blood stream was not invaded Very rarely there are multiple liver abscesses as in the case of Williams and Ovens[89] which recovered after operation on the gall bladder blood cultures were not made Schein[90] observed osteomyelitis of the dorsal spine The sputum in bronchopneumonia and the spinal fluid in meningitis may show the characteristic green color

A probable *diagnosis* may be made when the signs of septicemia are accompanied by diarrhea and a skin eruption of the sort described Positive cultures from the stools urine sputum or from lesions of the mouth or throat are proof of infection by the pyocyaneus but do not necessarily indicate septicemia The *latter is certainly present if cultures of the blood or the skin lesions are positive* A high agglutination titer greater than 1 160 has diagnostic value it is preferable to use the strain isolated from the patient since heterologous strains may give negative results

The *prognosis* is grave although occasionally mild cases are encountered chiefly in children

Treatment is unsatisfactory Cooper Cross and Lewis[91] found sulfanilamide and sulfapyridine of little benefit against infection of the peritoneum in mice possibly sulfadiazine might give better results and at present this is the drug of choice Penicillin is powerless against *B pyocyaneus*

Septicemia Due to *Micrococcus Tetragenus*

The *Micrococcus tetragenus* occurs frequently in the saliva of healthy persons and in the sputum in various diseases of the respiratory tract Although very pathogenic for mice its pathogenicity in the case of man as been denied by such authorities as Kolle and Wassermann who mention it only as a secondary invader in tuberculous cavities In spite of a growing literature on the subject very little attention is paid to it in textbooks on bacteriology and medicine While there is no doubt that it may occur in cultures as a contamination there seems to be sufficient evidence that it becomes at times pathogenic for man and is one of the causes of septicemia

The reasons for this belief are as follows the organism has been recovered not only in pure culture from the blood but has been found also in the pus of metastatic abscesses and has been demonstrated in sections of tissues In Castaigne s[92] case of septicemia following a leg injury *M tetragenus* was recovered in a state of purity from abscesses of the spleen and kidneys and was demonstrated in sections of tissue in the vicinity of these abscesses Reimann[93] in his case cultivated the organism from the blood spinal fluid and pus from the knee joint A high and increasing agglutination titer has been demonstrated notably in the case of Blum Vaucher and Karbiener[94] in which it rose to the figure of 1 2,000

The *Micrococcus tetragenus* has been found as the cause of localized suppurative processes viz bronchitis bronchopneumonia otitis meningitis peritonitis enterocolitis and arthritis The pus is abundant and viscid owing to the slimy character of the growth of this organism The first cases of septicemia in man were reported by Chauffard and Ramond[95] in 1896 Since then a number of cases has been published chiefly by Italian and French observers Two small epidemics were reported during the first World War among soldiers at the front in France one by Tremolieres and Loewe[96] the other by Birks Thomley and Fawcus[97] the clinical histories of the latter authors bear a strong resemblance to trench fever both in the presence of shin pains and in the absence of mortality, and it seems probable that their cultures were contaminated

The portal of entry usually is the respiratory tract or the tonsils, rarely external wounds or the bile passages The course is variable and does not differ essentially from that of septicemia due to other organisms There seems to be a predilection for involvement of the serous membranes especially the meninges joints and pleura Ulcerative endocarditis has been reported in a few cases

among them that of Adel[98] A macular eruption resembling that of typhoid fever may be present

Prognosis — The mortality in former days was 50 per cent Better results should be obtained with chemotherapy

Treatment — Long and Bliss[99] state that *M tetragenus* is markedly inhibited in its growth by sulfanilamide No references could be found to the action in vitro of the newer sulfonamides

In the absence of data as to the effect of penicillin we asked Dr J R Goerner of the New Haven Hospital staff to make test tube experiments Using two different brands of penicillin she found the organism to be inhibited by 0 0 and 0 01 units per c c respectively *M tetragenus* is therefore highly sensitive to penicillin

There are reports of 2 cases treated with sulfonamides those of Leach and Medinger[100] and of Criscitiello[101] in both of which a favorable effect was noted No cases treated with penicillin have been published Since *M tetragenus* is closely related to the staphylococcus it would seem that penicillin is the drug of choice

Septicemia Due to the Influenza Bacillus

The influenza bacillus *Hemophilus influenzae* is a gram negative bacillus which requires the presence of blood for its growth in cultures The group has been divided into *H influenzae* and *H parainfluenzae* The former requires both X and V factors for its growth the latter only the V factor Pittman[102] showed that pathogenic strains of *H influenzae* have a capsule containing a specific polysaccharide She was able to separate by means of precipitin and agglutination tests the pathogenic strains into two types A and B to which 4 more were added later viz C D E and F This is important for a potent antiserum for type B has been made by Alexander[103] this is the type concerned in most infections

Septicemia due to the influenza bacillus is not rare and is being recognized with increasing frequency Curiously enough it is seldom met with in connection with influenza It occurs chiefly among infants and young children The reason for this was disclosed by the work of Fothergill and Wright[104] They showed that the incidence of influenzal meningitis varied inversely with the bactericidal power of the blood Testing healthy subjects they found that in the most susceptible age group from 2 months to 3 years there was practically no bactericidal action against B strains derived from cases of meningitis from the ages of 3 to 10 years one third showed no action while all of those over 10 years of age had a high titer

In pediatric practice the disease is met with in 3 forms (1) as acute meningitis (2) as pharyngo-laryngitis with croup (3) as pneumonia with empyema In

fluenzal meningitis is associated with bacteriemia in close to 100 per cent, and therefore may be discussed here Almost all the cases are due to type B It is met with almost exclusively in infants and young children up to the age of 6 or 8 years In pediatric services the influenza bacillus ranks next to the meningococcus in frequency as a cause of meningitis

The onset is sudden and usually is preceded by an acute infection of the upper respiratory tract It differs from that of other forms of meningitis in the profound prostration which is evident The diagnosis depends upon finding influenza bacilli in the spinal fluid blood or nasal secretion An immediate diagnosis often is possible by examination of nasal swabs by the capsular swelling method similar to the Neufeld technic for typing pneumococci Purulent arthritis is a frequent complication rarely pericarditis is present as in the case of Kresky [105]

The syndrome of *acute pharyngo laryngitis with septicemia* was described first by Sinclair and Fousek[106] A single case in an adult had been reported previously by Lemierre[107] It is encountered almost exclusively in infants and young children The clinical picture is striking and easily recognized It often is preceded by an acute infection of the upper respiratory tract The onset is fulminating with sore throat and severe dyspnea due to laryngeal obstruction Fever and leucocytosis are present, but the outstanding feature is the profound degree of shock out of proportion to the dyspnea and persisting after the relief of the latter by tracheotomy There may be severe pain and dysphagia owing to inflammation of the epiglottis which is red and swollen The course in the absence of chemotherapy is rapidly down hill with death in 18 to 48 hours Of Sinclair and Fousek's[106] 10 patients 4 which were untreated died the remaining 6 all recovered with sulfonamides 2 receiving serum also All the reported cases have been due to type B

The third form occurs in infants with *pneumonia* and *empyema* due to the influenza bacillus and bacteriemia It often is complicated with meningitis

Influenzal septicemia in adults is rare The clinical picture is that of septicemia in general Most of the cases have been instances of subacute bacterial endocarditis Craven and associates[108] reported 2 cases of endocarditis and reviewed the literature They noted that all of those studied with sufficient care were due to *H parainfluenzae* but Rose[109] published later a case due to *H influenzae* type A Bourne and others [110] reported a case of open ductus arteriosus with bacteriemia treated by ligation and sulfapyridine a relapse 3 months later was cured by sulfapyridine

Frank[111] observed a very unusual instance of influenzal septicemia following peritonsillar abscess Other rare examples in adults are those of Lemierre and associates[107] laryngitis with septicemia, and 2 cases of Keefer and Rammelkamp[11] bacteriemia originating from cholangitis with stone in the common duct and from influenzal pneumonia

Prognosis — The outlook in influenzal meningitis and septicemia has improved vastly since the introduction of the sulfonamides and of serotherapy The mortality formerly nearly 100 per cent has been reduced to about 20 per cent in the case of meningitis and in the laryngeal group all of the reported cases recovered

Treatment — The sulfonamides in full doses are very effective Sulfadiazine is the drug of choice Alexander and her associates[113] have shown that the combined use of serum and sulfonamide is superior to that of either alone While the milder cases of meningitis recover with sulfonamides the use of serum in addition is necessary in severe infections In the laryngeal group sulfonamide alone usually is sufficient The serum employed should be anti influenza type B rabbit serum for horse serum is much less potent It is given in the case of children in the dose of 25 to 100 mgm nitrogen antibody preferably by vein Supplementary intrathecal injections sometimes are necessary In the laryngeal form an early tracheotomy usually is required

Septicemia Due to *Salmonella Suipestifer*

In recent years a considerable number of infections with *Salmonella suipestifer* has been reported This organism belongs to the paratyphoid group and is best known as a secondary invader in hog cholera Although its consideration properly belongs elsewhere it is discussed here in a brief way because it is not adequately described in most text books Salmonella infections are discussed also in Vol V Chapt XXI of Oxford Medicine

It was formerly thought to be the cause of hog cholera but later it was shown that this disease is due to a filterable virus with *Salmonella suipestifer* as a frequent but by no means constant secondary invader (for further discussion of swine fever see Vol V Chapt XVIII-C) Pathogenicity for man was noted first in the case of outbreaks of gastroenteritis in connection with contaminated food (for further discussion of food poisoning see Vol V Chapt XI-A) More recently it has been demonstrated as the cause of local infections purulent arthritis cholecystitis and of septicemia

Infection takes place in most cases probably by way of the alimentary canal following the ingestion of contaminated food In some epidemics of gastroenteritis the source has been infected pork eaten in a raw state in others no direct connection with diseased pigs could be traced although in the outbreak studied by Krumwiede Provost and Cooper[114] the tapioca pudding which was incriminated probably was contaminated by the cook while handling raw pork In most of the cases of septicemia the source of infection could not be determined although in a few cases in infants previous infection of the mother had taken place

Septicemia due to *Salmonella suipestifer* occurs with about equal frequency in

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formis Septicemia due to *Streptococcus putrificus* has been described already under the heading Septicemia Due to Anaerobic Streptococci

Septicemia Due to the Gas Bacillus

During the first World War gas gangrene was a common complication of wounds and not infrequently led to septicemia It was due usually to infection with one or more of the following three anaerobic bacilli or clostridia *Cl welchii Cl septicum Cl edematiens*

In civil practice septicemia due to a gas bacillus is almost always caused by *Cl welchii* although a few cases have been reported due to *Cl septicum* (*B oedematis maligni* of the Germans) The deadly *Cl oedematiens* resembles the diphtheria bacillus in that it acts by means of its toxin and very rarely invades the blood stream The following remarks will be confined to *Cl welchii* the gas bacillus par excellence

Clostridium welchii was first described by Welch and Nuttal in 189 and was named by them *B aerogenes capsulatus* Among the French it is known as *B perfringens* among the Germans as *B phlegmonis emphysematosae* or Fraenkel s bacillus It is a large gram positive rod usually provided with a capsule As shown by Bull and Pritchett[118] it produce an endotoxin which has interesting properties injected intravenously into animals it causes a tremendously rapid destruction of the red cells similar to that sometimes encountered in human cases injected into a muscle it causes necrosis and edema but no hemolysis in the blood stream it al o has an aggressive action paralyzing the local defense reactions of phagocytosis and bacteriolysis contraction of unstriped muscle fibers takes place with diarrhea

The gas bacillus has a wide distribution in nature it is present in most samples of soil and is a regular inhabitant of the intestine of man and animals It is present in the vagina of 50 per cent of healthy women according to Schottmuller[119] Those interested in the bacteriological aspects should read the extensive monographs of Weinberg and Seguin[1 0] and of the Medical Research Council[1 1]

Infections with the gas bacillus usually are localized and most frequently involve the extremities in the form of gas gangrene or gas phlegmon Gas gangrene occurs in contaminated wounds in which there has been extensive destruction of muscle Not infrequently the pregnant uterus is infected leading usually to endometritis sometimes to infection of the placenta with emphysema of the fetus Gas may form in the uterine cavity tympania uteri and may escape in an explosive manner when the cervix is dilated These conditions are not serious for the mother If however the uterine wall is involved septicemia almost always results and the mortality is very high The gas bacillus is a rare invader in the case of local infections of the urinary tract either alone or with other bacteria

adults and in children, in the latter it affects chiefly infants and younger children up to the age of six In adults the course most often resembles that of paratyphoid fever There is abdominal distension often accompanied by pain and vomiting and peritonitis may be simulated Since there are no gross intestinal lesions hemorrhage and perforation do not occur Diarrhea is noted rather frequently The spleen often is palpably enlarged but rose spots have not been reported Leucocytosis is absent in uncomplicated cases and leucopenia often is noted the polynuclears are not increased The blood findings are therefore, the same as those in typhoid and paratyphoid fever A metastatic abscess of the spleen was reported by Walker, Weiss and Nye[11] with recovery after incision and drainage In another large group the course is that of a severe infection of the respiratory tract with the signs of bronchopneumonia

The mortality is high in adults 57 per cent but probably is lower than this in reality, as the milder cases are likely to be overlooked

In children the course is somewhat different It is apt to be much shorter, being only 6 days *in a series of 7 cases of Kuttner and Zepp*[116] *in the cases with* bronchopneumonia however the duration is much longer There is a pronounced tendency to suppurative arthritis which in some cases has been secondary to osteomyelitis This is in keeping with the well known frequency of osteomyelitis in the young A case with endocarditis was reported by Goulder[117] Hemorrhagic purpura with thrombocytopenia occurred in one of Kuttner and Zepp s[116] cases

The mortality is very much lower in children than in adults, being only 14 per cent

The *diagnosis* should be suspected in cases resembling typhoid fever in which the agglutination reactions for typhoid and paratyphoid are persistently negative It depends upon the isolation of *Salmonella suipestifer* from the blood or from the pus of metastatic lesions Stool cultures usually are negative those of the urine may be expected to be positive if cystitis is present The identification of *Salmonella suipestifer* requires the services of an expert bacteriologist The presence of agglutinins in the patient s serum has diagnostic value but often is delayed until after convalescence

Treatment is symptomatic Sulfonamides are not beneficial and penicillin is without effect

Septicemia Due to Anaerobes

Infection of the blood stream with anaerobes is being reported with increasing frequency since the use of appropriate culture methods has become more general The most important anaerobic organisms are *Streptococcus putrificus* and the gas bacillus group (*Cl welchii Cl septicum Cl oedematiens*) Others occasionally encountered are *B fundiliformis, B pyogenes anaerobius B fragilis* and *B fusi*

bimanual examination although it is usually present if the uterus be felt during a laparotomy Gas bubbles rarely are present in the lochia although this is quite common in cases of emphysema of the fetus The lochia often are foul but this is due to the associated bacteria of putrefaction and not to the gas bacillus itself Extension to the peritoneum is the rule in gas gangrene of the uterus there is a scanty hemorrhagic exudate but the symptoms and signs of peritonitis are not well defined

Prompt *diagnosis* is important A smear from the cervix should be examined in every case of infected abortion The finding of large gram positive rods indicates with a high degree of probability the presence of the gas bacillus Gas bubbles in the lochia are an almost certain sign of infection of the uterine contents with *Cl welchii* but usually are lacking in cases where the musculature of the uterus is involved Foulness of the lochia usually indicates a septic endometritis the evil smell being due either to *Streptococcus putrificus* or to other putrefactive bacteria with which the gas bacillus may be associated The gas bacillus of itself causes either no odor or a faintly rancid one *Cl welchii* often may be found in the urinary sediment in case the blood stream has been invaded Crepitation of the uterus is a pathognomonic sign but is rarely obtainable before the abdomen is opened The syndrome of bronzing of the skin with hemoglobinuria anemia and cyanosis is almost pathognomonic of gas bacillus septicemia but by the time it has developed fully usually it is too late to save the patient

During the first World War septicemia was a fairly common complication of gas gangrene of the extremities In fact Weinberg and Seguin state that all of the fatal cases examined by them showed positive blood cultures provided they were due to *Cl welchii* *Cl septicum* also was always present in the blood in fatal cases due to this organism but *Cl oedematiens* though highly pathogenic mortality 50 per cent seldom could be cultivated from the blood The clinical picture was as follows there was air hunger due partly to acidosis partly to anemia the pulse was rapid out of all proportion to the temperature the mind remained clear to the end Fever was present except in fulminating cases Jaundice and anemia were noted fairly often but the combination of bronzing with hemoglobinuria so frequent in the post abortive group was almost never met with

Prognosis — In gas gangrene of the extremities the mortality varies from 40 to 60 per cent It is lower in cases receiving the benefit of early surgery serum and penicillin probably about 25 per cent In post abortional cases Hill using serum only noted a mortality of 63 per cent It should be lower now that chemotherapy is available

Treatment — In gas gangrene complicating wounds thorough excision of the affected muscles is imperative Amputation should be avoided if possible The use of polyvalent serum is helpful and should be started immediately without waiting for the results of cultures It is best given intravenously in doses of at

and is one of the sources of pneumaturia It is the cause of the "foamy organs found now and then at autopsy but this gas formation takes place after death and has no clinical importance

In civil practice septicemia due to the gas bacillus occurs chiefly in connection with infected abortions and less often as a puerperal condition at term Its frequency varies greatly in different places and at different times For example Hill[122] reported 30 cases from a Melbourne hospital occurring within a period of 2 years His article is the most comprehensive one or the subject Heim[123] observed 7 cases in 11 months In general it is not a common event deaths due to the gas bacillus accounting for about 5 per cent of the mortality from post abortional septicemia Rendle Short[124] reported 6 cases and reviewed the literature

Other much rarer sources of septicemia are contaminated hypodermic injections of which Junghanns[125] has collected 60 instances, and infection from the intestines which carried off a valued member of the New Haven Hospital staff as a complication of intestinal obstruction

The clinical picture differs from that of septicemia due to other organisms chiefly owing to the hemolytic action of the toxin and the local production of gas

Injury to the uterus apparently is a necessary preliminary to infection The usual story is that of a self induced abortion followed within a few hours or days by the sudden onset of cramp-like abdominal pains, diarrhea, vomiting and bleeding from the uterus Fever is present but usually not high the pulse is very rapid out of proportion to the other signs of infection In some, but by no means all cases an extraordinarily rapid hemolysis takes place in the blood stream identical with that produced in animals by the intravenous injection of the endotoxin of *Cl welchii* This gives rise to a typical clinical picture rarely met with in any other condition jaundice and anemia come on with great rapidity the blood count often falling one million or even two in the course of a few hours The skin takes on a peculiar hue varying from a brownish yellow to mahogany, depending upon the varying proportions of methemoglobin, oxyhemoglobin hematin and bilirubin which are present in the plasma The urine is very scanty, owing to blocking of the tubules with hemoglobin and is turbid and brownish black in color The rapid dissolution of the blood leads to anoxemia with cyanosis and dyspnea A high leucocytosis with marked shift to the left and the appearance of myelocytes and normoblasts in the blood bears witness to the tremendous stimulation of the bone marrow Death takes place within 48 hours in over one third of the cases according to Toombs[126] If the course is less fulminating death may occur later with anuria and uremia The blood culture almost always is positive usually pure often mixed with *B coli* streptococci or staphylococci Rarely *Cl septicum* is the cause of the septicemia Physical examination often shows tenderness over the uterus but gas crepitus seldom is to be elicited by

to collect 20 French cases In the United States in recent years a number of articles on the subject have appeared reference to which may be found in the publication of Smith and Ropes[135] Those interested in the bacteriology should consult the encyclopedic work of Weinberg Nativelle and Prevot[136]

Experimental reproduction of the disease has been successful in the hands of Teissier[138] and of Thompson and Beaver[137] Metastatic abscesses were noted often having the same localization as in the patients from which the strains were derived

The portal of entry most frequently is the tonsils occasionally the intestine or the genitourinary tract The onset usually is preceded by a peritonsillar abscess The course is apt to be short and stormy with chills high fever and marked toxemia Metastatic abscesses almost always are present In the cases arising from the throat thrombophlebitis of the internal jugular vein is frequent and the metastases are situated in the lungs and joints abscesses in the neck and empyema are common complications Occasionally meningitis or abscess of the brain is noted When the portal of entry is the intestine multiple abscesses of the liver are the rule Dixon and Deuterman[138] reported 5 cases following operations for carcinoma of the colon all of which had liver abscesses and usually purulent thrombosis of the inferior mesenteric or portal veins Jaundice usually is present if there are abscesses in the liver and is not uncommon in other cases Anemia is a striking feature and may be referred to the hemolytic action of the bacterium In the lungs there are necrotic nodules and small infarcts which go on to abscess formation Gas in the soft tissues of the arm with crepitation was noted in one of Smith's[135] cases In Teissier's[137] first case there was a vesiculopustular rash on the legs from which *B funduliformis* was recovered on pure culture

The *diagnosis* may be suspected if following a peritonsillar abscess there develops signs of septicemia with abscesses of the lungs and joints or if after an operation for cancer of the colon there are indications of a hepatic abscess It is confirmed by the results of anaerobic blood cultures or by the recovery of the organism from metastatic lesions

The *prognosis* is very bad mortality ranging from 70 to 90 per cent if cases with transient bacteremia are excluded

Treatment — Up till recently the treatment has been unsatisfactory Ligation or excision of the internal jugular vein often is indicated also drainage of any accessible collection of pus Prevot[139] has shown experimentally that the sulfonamides are efficacious and they should be employed in large doses enough to maintain a level of 15 mgm per 100 c c So far only 3 cases of recovery with sulfonamides have been reported by Brown[143] Goodnough[141] and Reid[14-] Sulfadiazine is the drug of choice Penicillin is not indicated Frequent blood transfusions are necessary on account of the anemia

least 50 000 units repeated every 8 hours Sulfonamides are definitely beneficial but penicillin is better as shown by the experimental work of Hac[127] and by experience on the field as reported by Jeffrey and Thomson[128] and by Cutler[129] In the case of *Cl septicum* however McIntosh and Selbie[130] found that in vitro sulfathiazole was superior to penicillin and much better than sulfadiazine Clinical experience with infections with *Cl septicum* is very limited, but these experiments suggest that a combination of sulfathiazole with penicillin might be the best treatment

Since penicillin is not antitoxic the use of serum cannot be dispensed with Transfusions of blood are essential to combat the intense anemia To sum up treatment should include surgery serum penicillin and transfusion

The medical treatment of post abortional and puerperal septicemia is similar except that the appropriate univalent serum should be employed instead of a polyvalent one This almost always will be an antiserum for *Cl welchii*, since infections with other members of the group though fairly common in war wounds are extremely rare in civil life

Surgical treatment in post abortional cases until recently called for immediate hysterectomy if gas gangrene of the uterus was present With the use of serum and penicillin it may be possible to avoid this measure In puerperal cases hysterectomy is contraindicated on account of the very high operative mortality

Septicemia Due to the Bacteriodes Group B Funduliformis B Fragilis, B Gonidiaformans and B Pyogenes Anaerobius (*Buday s Bacillus*)

The genus *Bacteroides* is characterized by motile or non motile gram negative rods without endospores All the members are obligate anaerobes The most important in human pathology are *B funduliformis*, *B fragilis* and *B pyogenes anaerobius*

Bacteroides funduliformis formerly regarded as occurring only in local infections has been found to be a cause of septicemia It was first described by Halle[131] in 1898 as occurring in the uterine culture of healthy puerpera and in the pus of abscesses of Bartholin s gland Since then it has been demonstrated in the healthy intestine vagina and pharynx and often associated with putrefactive organisms in tonsillitis otitis media cholecystitis appendicitis and in infections of the genitourinary tract

B funduliformis appears in the animal body in the form of small gram negative rods with bipolar staining but in cultures it displays a remarkable pleomorphism large spherical bodies long filaments and cocco-bacillary forms combine to give a variegated picture It is strongly hemolytic In cultures it produces gas with a fetid odor but it is not a cause of putrefaction or gangrene

The first case of septicemia was reported by Teissier[132] in 1929 Two years later the same author[133] published 3 more cases, and Lemierre[134] in 1936 was able

was described first by Tunnicliff and Jackson[147] in 1925 It was isolated from a tonsillar plug It is closely related to *B fundiliformis* from which it differs in the appearance of round bodies composed of chromatin which are interpreted as gonidia As a cause of septicemia it is rarely met with the only 2 cases in the literature being those of Reid and associates[14] The clinical course is the same as that of septicemia due to *B fundiliformis*

Septicemia Due to Vincent s Organisms

B fusiformis occurs in the form of slightly bent rods with pointed ends and is gram negative It is strictly anaerobic and grows only in media containing animal protein developing a putrid odor but no gas It is found most often in Vincent angina (see Vol V Chapt I-A) and ulcerative stomatitis trench mouth always in association with spirochetes It is also present frequently in gangrenous processes in various parts of the body in appendicitis gangrene of the lung empyema balanitis puerperal endometritis noma and hospital gangrene sometimes in pure culture In metastatic abscesses of the viscera long whip-shaped threads are observed The identity of the fusiform bacillus and Vincent s spirochete is still an open question

In rare instances *B fusiformis* gives rise to metastatic abscesses and a clinical course like septicemia so that its inclusion here seems justified Ghon and Mucha[148] were the first to report septicemia due to this organism Most of the cases have been infected from the intestine where *B fusiformis* is a frequent guest and have followed appendicitis or in one instance a perirectal abscess Occasionally bronchiectasis or otitis media has constituted the primary focus Metastatic abscesses occur usually in the liver or brain sometimes in the spleen or kidneys In the case of Rosenow and Tunnicliff[149] following an appendiceal abscess there were abscesses of the lungs infarction of the spleen and multiple periostitis and osteomyelitis The pus has a peculiar fetid odor Maresch[150] in 1916 reported 5 cases and reviewed the literature

Blood cultures have been positive in 3 cases only In that of Larson and Barron[151] there was necrosis of the jaw with gangrene of the soft tissues due to infection with Vincent s organisms The spleen was greatly enlarged the other organs were normal A blood culture taken 2 days before death showed fusiform bacilli but no spirochetes Williams[152] reported 2 cases in which the fusiform bacillus and spirochetes were cultivated from the blood Both were cases of arthritis the first chronic with acute febrile exacerbations the second acute In the first case in which cultures were positive on 11 occasions there were complications with gonorrheal urethritis and brucellosis The second case followed the bite of a rat an animal known to harbor fusospirochetes

Treatment — In the past intravenous injections of neoarsphenamine have

Septicemia Due to Bacteroides Fragilis — This organism differs from *B fundultformis* in that it is neither pleomorphic nor hemolytic It differs also in that it is much less frequent as a cause of septicemia and is less fatal the mortality being about 30 per cent The clinical course and treatment are the same as in the case of *B fundultformis*

Septicemia Due to Bacteroides pyogenes anaerobius (Buday s bacillus) — This bacterium is identical with *B fundultformis* in morphology but differs from it in requiring the presence of serum for its growth and in the production of H_2S in cultures It was first described by Buday[143] in 1916 It was found to be the cause of a small epidemic occurring in Hungary during the first World War among soldiers with chronic discharging wounds of the extremities usually involving the bones Bogdan[144] described 24 such cases Up until recently the disease had not been found outside of Hungary but the report of 6 cases from Germany by Hegler and Nathan[145] shows that it may be expected elsewhere Case 4 of these authors is identical with that previously reported by von Gusnar and Globig[146] The bacillus is remarkable chiefly for its preference for the liver which is shown not only in the human disease but following inoculation of animals rabbits It is this high pathogenicity which distinguishes it from other gram negative anaerobes A second interesting feature is that almost without exception the septic focus was a deep infected wound usually involving bone In 2 of Hegler s cases from civil life the tonsils were the portal of entry, the 4 remaining cases followed infected fractures of the nasal bones (2) of the finger (1) and of the tibia (1) Abscess of the liver occurred in almost all the Hungarian cases and in all but the 2 tonsillogenic cases of Hegler and Nathan These abscesses may be either single or multiple they are due to infection via the hepatic artery as shown by the absence of lesions of the portal vein or its tributaries Hegler and Nathan found thrombosis of a hepatic vein in _ of their cases showing that this bacillus is one of the organisms capable of passing the liver filter

The course is either acute or subacute All of the acute cases died but those that were subacute recovered The acute type is characterized by high fever, usually remittent or intermittent chills and signs pointing to involvement of the liver The latter include severe pain in the right shoulder, jaundice hepatic tenderness and enlargement The lungs too are involved often with indications of bronchopneumonia and putrid abscesses which may progress to empyema Purulent arthritis is not uncommon

The *diagnosis* may be suspected when an infected fracture is followed by chills fever and signs pointing to involvement of the liver It may be confirmed by the results of culture of the blood or of the pleural or joint exudates Inoculation into animals of cultures or of infected material will reproduce the disease Th *treatment* is the same as that of infection with *B fundultformis*

Septicemia Due to Bacteroides Gonidiaformans — *Bacteroides gonidiaformai*

surgical treatment pulmonary abscesses are not seen as often now as they used to be

The work of Libman[155] showed that the streptococcus is the chief cause of sinus thrombosis Out of 43 cases he obtained positive blood cultures in 34 or 80 per cent Of the 34 positive cases 30 showed the hemolytic streptococcus and 3 pneumococcus type III the remaining case being one of proteus infection The bacteriology of sinus thrombosis is therefore much simpler than that of otitis media in which a considerable variety of organisms has been found The clot in the sinus usually shows streptococci sometimes it is sterile

The *clinical picture* is quite definite Usually a chill is the earliest and most characteristic symptom Pain often is present and is more severe and deeper seated than the pain of otitis media or mastoiditis usually it is located above the region of the mastoid The fever is apt to be higher than it is in simple otitis and the symptoms of toxemia are more pronounced The temperature chart is not characteristic it may show the continuous the remittent or the intermittent type The chills may be repeated frequently or there may be only a single rigor at the onset There is usually a marked leucocytosis A foul diarrhea sometimes occurs Extension of the thrombosis to the jugular vein is a late event and may be manifested by the presence of a hard tender cord in the neck often associated with stiffness and pain in the neck Metastases also are of relatively late occurrence and are seen clinically chiefly in the subcutaneous tissues and the lungs occasionally in the joints very rarely in the endocardium A hacking cough is the earliest sign of pulmonary involvement Meningitis if it occurs gives rise to the usual signs but a complicating cerebral abscess often remains silent The eye grounds show either hyperemia of the disc or optic neuritis in about 25 per cent of the cases of sinus thrombosis

The *diagnosis* of otogenous septicemia is to be suspected in all cases of otitis media or mastoiditis in which the fever and signs of toxemia are out of proportion to the local findings especially if a chill has occurred and pain has become more severe and of a different quality than that experienced earlier Under these circumstances operation on the mastoid should be performed at once if this has not already been done and the lateral sinus should be inspected Blood cultures should be taken and if positive constitute an absolute indication for immediate exploration of the mastoid and of the sinus negative blood cultures are of course no reason for delaying operation as the sinus may be thrombosed but not discharging bacteria into the blood stream A positive blood culture usually indicates sinus thrombosis although Kopetzky[158] found streptococci in the circulating blood in the absence of sinus thrombosis in all of his 7 cases of osteothrombotic phlebitis complicating hemorrhagic mastoiditis

A single chill may occur at the onset in simple mastoiditis or may be the first symptom of erysipelas of the operative wound following mastoidectomy Re-

been successful in a few cases The sulfonamides and penicillin merit a trial in view of their efficacy in Vincent's angina No in vitro tests have been published

OTOGENOUS SEPTICEMIA

Septicemia starting from the ear usually is the result of phlebitis or thrombosis of the lateral sinus although not infrequently it occurs without involvement of the sinus in the hemorrhagic type of acute mastoiditis with osteophlebitic thrombosis of the veins of the walls of the mastoid cells as shown by Kopetzky[153] More rarely there is direct invasion of the blood stream from the middle ear or mastoid without venous thrombosis Occasionally the jugular bulb is the seat of primary thrombosis by extension downward through the floor of the tympanic cavity or one of the petrosal sinuses is affected by extension of an inflammatory process in the petrous bone in which latter case the thrombus frequently is propagated to one or both of the cavernous sinuses

Thrombosis of the sigmoid sinus is almost always a result of mastoiditis, occasionally it complicates otitis media without involvement of the mastoid cells There are two ways in which the sinus may become involved, (1) by invasion from without from a neighboring perisinus abscess, especially in the coalescent type of mastoiditis in which the cell walls break down and frank suppuration occurs, (2) by extension of the thrombosis in one of the small veins emptying into the sinus most frequently in the hemorrhagic form of mastoiditis There may be only phlebitis of the wall of the sinus or a mural thrombus may be present without occlusion of the lumen Not infrequently bacteria penetrate the wall of the sinus from a perisinus abscess without any apparent lesion of the vessel In about 50 per cent of cases of sinus thrombosis coming to autopsy the internal jugular vein is involved also Sinus thrombosis occurs alone in one half of the fatal cases in the remainder it is associated with meningitis or cerebral abscess or both It is about equally common as a complication of chronic or acute otitis media It should be emphasized that many cases of otogenous septicemia are met with in which the sinus is not implicated

The persistence of the infantile type of mastoid with few cells constitutes an important predisposing factor to mastoiditis and, therefore indirectly to sinus thrombosis

The pathology of otogenous septicemia differs from that of other forms of streptococcus blood infections only in the frequency with which metastases occur This is readily explained by the breaking off of emboli during the process of softening of the thrombus Thus Hessler[154] in a large series found metastases in two-thirds most frequently in the lungs the size of the emboli usually preventing a passage through the pulmonary capillaries It should be noted however that the detachment of emboli is a late event in sinus thrombosis so that with modern

as erysipelas starting from the operative wound after mastoidectomy septicemia arising from sources other than the ear pneumonia pyelitis etc

In the *treatment* of otogenous septicemia surgery occupies a very prominent place The brilliant pioneer work of Macewen[159] and of Horsley in Great Britain and of Jansen[160] and others in Germany has reduced the mortality from 90 per cent to 25 per cent For details the otological literature should be consulted

The advent of chemotherapy has not removed the necessity for surgical intervention but has lowered the mortality still further While the sulfonamides have proved effective recent work with penicillin has shown that this drug is superior in the case of the streptococcus which is the organism chiefly concerned

PUERPERAL SEPTICEMIA

Septicemia following full term delivery and abortion although usually preventable even now is far too common The infection almost always is introduced from without and is most frequent after criminal abortions instrumental deliveries and unclean vaginal examinations or streptococci may be transferred to the patient directly or indirectly by attendants or members of the family who are suffering from streptococcic infections such as scarlet fever erysipelas otitis media and inflammations of the nose and throat streptococcus carriers without inflammatory lesions probably are far less dangerous Occasionally the puerpera is herself the subject of streptococcus disease in some part of the body other than the genital tract and may infect herself by handling the genitalia the hematogenous route in such cases is extremely unlikely The air of wards in which septic cases are treated has been shown to contain streptococci and air borne infection is a possible although probably a rare event

The condition of the genital tract after parturition is especially favorable to infection The placental site represents a large wound surface and the whole interior of the uterus is devoid of epithelium the regeneration of which is not complete until two weeks have elapsed The cervical canal practically closed at other times is patulous and offers a ready path for the invasion of germs The uterus often contains placental remains fragments of membrane and blood clot which by obstructing the drainage of the organ facilitate multiplication of bacteria and offer a most favorable culture medium In about 95 per cent of deliveries wounds of the vulva vagina or cervix exist offering still further opportunities for infection

Predisposing causes are marked exhaustion preceding chronic disease and the character of the labor premature rupture of the membranes renders possible the infection of the amniotic fluid prolonged and obstructed labor predisposes on account of the more extensive bruising of the tissues and exhaustion of the patient as does placenta previa by reason of the abnormal site of the placental attachment near the cervix and the frequent necessity for operative procedures

peated chills indicate with almost certainty infection of the blood stream The local signs usually are only those of inflammation of the middle ear and mastoid and are of little assistance in making the diagnosis of sinus thrombosis Edema over the mastoid process is fairly common in uncomplicated mastoiditis, although extensive edema spreading upwards above the ear is an important, although rare, indication of sinus thrombosis *Griesinger's sign* The internal jugular vein when thrombosed is seldom palpable

Crowe s sign[156] is helpful in the diagnosis of sinus thrombosis It depends upon the fact that with unobstructed venous circulation it is necessary to compress both jugular veins at once to produce dilatation of the veins of the retina whereas if one lateral sinus is thrombosed unilateral pressure on the healthy side of the neck will produce the phenomenon while pressure on the diseased side is without effect

The *Tobey Ayer test*[157] rests on the same principles but requires lumbar puncture and measurements of the pressure of the spinal fluid Pressure is made alternately over each internal jugular vein and then on both veins simultaneously noting the effects on the spinal fluid pressure If the sinus is obstructed compression of the vein on the unaffected side causes a prompt and marked rise in pressure equal to that when both sides are compressed together, and there is a prompt drop in pressure when the compression is released Compression of the vein on the diseased side shows either no rise in the manometer or more frequently a slow rise of only 10 to 20 mm Incomplete occlusion of the sinus gives intermediate results usually with enough difference in the rise of pressure between the two sides to be conclusive The test has been modified in the following way, the manometric pressure is first increased by bilateral jugular compression and then the effect of release of each jugular vein is observed separately (personal communication by Dr Ayer) If the technique is carried out properly, the presence or absence of thrombosis of the lateral sinus and the side affected can be determined with a high degree of accuracy Occasional false negatives occur, especially in obese subjects in whom the vein is difficult of compression An objection to this test is the possible danger that lumbar puncture in the presence of an infected blood stream may lead to meningitis This fear is based on the experimental work of Weed[158] on animals and not so far as we are aware on clinical experience in the case of man However in some clinics a positive blood culture is considered a contraindication to lumbar puncture unless signs of meningitis are present already The Crowe test and the Tobey Ayer test are especially valuable in the rare instances of primary thrombosis of the jugular bulb in which surgical exploration of the lateral sinus often is negative

The demonstration of metastasis usually in the lungs joints or subcutaneous tissues is proof of septicemia even if blood cultures are negative

In the *differential diagnosis* it is necessary to exclude other causes of fever such

only fatal cases Other authors report occasional fatal cases of puerperal sepsis due to the colon bacillus In rare instances almost any of the bacteria found in other forms of septicemia may be respon ible (Friedlander s bacillus *Micrococcus tetragenus*, gonococcus etc) It is possible that the high percentage 25 per cent of staphylococcic infection in Schottmuller s series is due to the preponder ance in his material of septic abortions over postpartum infections at term Unfortunately no large series is available with separation into these two groups

The infection of the blood stream usually takes place from the body of the uterus especially from the placental site Lenhartz working with autopsy material reckoned 75 per cent by this channel and the remaining 25 per cent through wounds of the vulva vagina or cervix

Excluding those instances in which bacteria are found only temporarily in the blood the cases may be divided into three groups according to the condition of the uterus and its appendages (1) the thrombophlebitic form with thrombosis of the local veins often extending into the internal iliac or ovarian veins (2) the lymphangitic form in which the lymphatics of the uterus and broad ligament show inflammatory changes accompanied usually by parametritis and (3) septicemia without thrombophlebitis or lymphangitis

Thrombophlebitic septicemia is met with in about 50 per cent of the fatal cases It occurs in an acute form due usually to the hemolytic streptococcus or the staphylococcus and a subacute form due almost always to the anaerobic streptococcus (see section on Septicemia Due to Streptococcus) Thrombosis starts as a rule from the venous sinuses at the placental site and spreads either by way of the lower uterine veins into the uterine plexus and the internal iliac the hypogastric vein of continental writers or through the upper uterine veins to the ovarian vein or both Purulent softening of the thrombus often occurs with the dislodgement of emboli which accounts for the relative frequency of metastases in this type of septicemia and for the fact that they are situated most often in the lungs Metastases in other viscera the muscles and about the joints are not uncommon Panophthalmitis may occur Often there is a sterile serous effusion in the vicinity of a purulent exudate e g in the pleura in the case of peritonitis in the joints with periarticular abscesses Generalized peritonitis is common occurring in 40 per cent (Lenhartz) It takes place usually by direct extension from the parametrium through the wall of the uterus or from rupture of a parametric abscess much less often it occurs by extension through the tubes or in more remote ways such as rupture of a metastatic abscess of the spleen Acute endocarditis is common Meningitis is unusual

The *lymphangitic form* usually is due to the hemolytic streptococcus much more rarely to the gas bacillus which however always invades in this way At times the staphylococcus causes a purely lymphatic form Infection takes place most often from lacerations of the cervix or vagina with extension into the broad

From the healthy vulva and vagina a variety of organisms has been cultivated Schottmuller has found the anaerobic streptoccus to be a constant inhabitant of the vagina even in children The vagina contains relatively few organisms during the first twenty four hours after child birth, but beginning with the second day they are present in large numbers especially the anaerobes Hemolytic streptococci are to be found in the vagina in about 3 per cent of women at the onset of labor, but Lancefield and Hare[161] have shown that these are strains which are only feebly pathogenic for man, and which differ from the strains causing puerperal sepsis Other recent work has made it plain that in the case of the hemolytic streptococcus the infection of the puerpera does not come from organisms harbored in the vagina but from without For a full discussion of the question the reader is referred to an article in 1936 by Colebrook[167]

In localized postpartum infections the streptococcus is the most common causative organism Contrary to the usual statement the anaerobic *Streptococcus putrificus* is just as often the cause of the trouble as the *S hemolyticus* Harris and Brown[45] in 113 cases of streptococcic puerperal infection found anaerobic and aerobic streptococci in cervical smears with equal frequency, no cases of septicemia were included in this series Other organisms often are associated especially the colon bacillus the staphylococcus and the gas bacillus The gonococcus is a fairly common cause of localized postpartum infection, but it is almost never the cause of puerperal septicemia

In putrid endometritis as Schottmüller has shown the causative organism usually is the anaerobic *Streptococcus putrificus* It produces sulphurated hydrogen in media containing serum or blood hence the odor The colon bacillus and the gas bacillus also may cause endometritis with an ill smelling discharge in the case of the latter the odor is due to associated putrefactive bacteria

Puerperal septicemia formerly was regarded as almost entirely due to *Streptococcus hemolyticus* This is no longer the opinion In the large series of 14 fatal cases of Schottmuller and Bingold[12] the anaerobic *S putrificus* accounted for almost as many cases as the *S hemolyticus*, while the staphylococcus was not far behind For the cases showing a single infective organism their figures were as follows *S hemolyticus* 34 per cent *S putrificus* 32 per cent, *Staphylococcus aureus* and *albus* 25 per cent, gas bacillus 7 per cent pneumococcus 1 5 per cent anaerobic staphylococcus 0 8 per cent There were no cases due to the colon bacillus alone but of the mixed infections of which there were 13 9 per cent of the total 142 cases 3 showed the presence of this organism *Streptococcus viridans* was never found alone but occurred 3 times in association with other bacteria It is evident from these figures that the pyogenic cocci are the cause of the vast majority 91 per cent of the cases of puerperal septicemia Infections with the colon bacillus in pure culture are not very rare but usually go on to recovery and therefore are not represented in Schottmuller and Bingold s series, which includes

uterus if infected usually will show delayed involution and may have a boggy feel A tender resistant mass lateral to the cervix usually is due to parametritis while at times thrombosed veins may be palpated in the broad ligament as tender cords Generalized peritonitis in the puerperium differs from other forms in that owing to the overstretched condition of the abdominal walls distension is greater and abdominal rigidity less or even absent and in the frequency of diarrhea Anemia often is present In puerperal infections with the gas bacillus a characteristic syndrome is encountered consisting of a precipitate fall of the red count with a peculiar brownish jaundice and hemoglobinuria The leucocyte count is variable It should be borne in mind that a leucocytosis of 10 000 to 20 000 normally exists during the early part of the puerperium The differential count however in the healthy puerpera is normal or shows an increase of lymphocytes while in the infected the neutrophiles almost always are increased It should be emphasized that in many cases of puerperal septicemia normal or even subnormal counts are met with

Skin rashes occur occasionally usually as petechiae or transient areas of erythema It is often stated that scarlatiniform rashes are common We believe that most of such cases simply were instances of scarlet fever occurring in the puerperium In our experience almost without exception the case has turned out to be one of scarlet fever as shown by the desquamation the appearance of the tongue and throat and the occurrence of other cases in the vicinity It should be noted however that in puerperal scarlet fever in the strict sense the primary lesion is in the genital tract and sore throat and tonsillitis are lacking

Fever above 100° F during the puerperium is always abnormal and calls for a careful examination It should not be ascribed to mastitis unless there is definite pain tenderness and localized swelling in the breast If a complete physical examination reveals no disease outside of the pelvic organs postpartum infection should be suspected and with strict aseptic precautions the parts should be examined with a speculum and a bimanual examination made Some authors advise against any sort of pelvic examination during the early days of the puerperium on account of the possibility of spreading the infection but with proper care and gentleness there should be no risk The lochia should be examined a foul odor indicating infection of the uterine cavity with anaerobes Gas bubbles point to the presence of the gas bacillus but are present chiefly in localized infections rarely in septicemia due to *Cl welchii* The bacteriological examination of the lochia or uterine contents often is helpful if made early in the disease although it may be misleading Blood cultures are almost a sine qua non for diagnosis if negative for aerobes or if putrid endometritis is present anaerobic methods should be employed

The differential diagnosis between local infection and septicemia depends largely on the difference in the severity of the symptoms the former running

ligament or pelvic cellular tissue through the lymphatics, which may be found filled with pus at autopsy Abscess formation in the parametrium or pelvis often takes place and this form of postpartum infection leads more frequently to generalized peritonitis than to septicemia Frequently however, both are present Metastases with the exception of acute endocarditis usually are lacking In the third type there is septicemia starting from infection of the vagina cervix or endometrium but without thrombophlebitis or lymphangitis This group includes many of the fulminating cases

The relative frequency of the lymphogenic and the thrombophlebitic forms is difficult to estimate for often they are combined and it may be impossible to tell at autopsy which was the primary event Sommer[163] in a careful survey of an extensive autopsy material finds evidence of lymphangitis in the majority of cases and considers that the associated thrombophlebitis usually is secondary His reasons for this belief are that the thrombosis often begins at a considerable distance from the uterus and adnexa and shows evidence of penetration of the wall of the vein from without inwards also because the thrombus often is free from bacteria and therefore could not be the source of infection of the blood stream In his experience it was exceptional to find a continuous propagated thrombus starting in the veins of the uterine wall and extending into the larger veins

The *clinical course of puerperal septicemia* may be described as a whole noting peculiarities due to the type of infection For the description of puerperal infections due to anaerobic streptococcus and the gas bacillus the reader is referred to the sections on Septicemia Due to Streptococcus and on Septicemia Due to Anaerobes The onset usually is abrupt with a chill, but sometimes a staircase form of chart is seen the temperature rising gradually The first symptoms sometimes appear within a few hours of labor and usually within the first week Occasionally in the thrombophlebitic form the onset is delayed beyond this period up to the fourteenth day The fever usually is high with marked remissions less often it is intermittent and occasionally continuous Daily chills often are noted especially in the thrombophlebitic form The course may be short and stormy or protracted A subacute type with frequent chills intermittent fever and metastatic abscesses in the lungs is the rule in infections with the anaerobic *Streptococcus putrificus* Jaundice is seen at times especially in gas bacillus infections The spleen is enlarged and usually palpable Systolic mitral murmurs are common even in the absence of endocarditis The pelvic examination often reveals on inspection wounds of the vulva vagina or cervix, and they may be covered with a dirty grayish exudate The lochia in pure streptococcus infections are sweet a foul odor indicates putrid endometritis, which may be associated with a general infection due to the *Streptococcus putrificus* the gas bacillus or the colon bacillus or on the other hand hemolytic streptococci or staphylococci may be the sole invaders of the blood stream On palpation the

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usually a milder and shorter course In the case of septic abortions the onset may be violent, but the local nature of the infection usually is shown by the remarkable improvement after evacuation of the uterus, the temperature often returning to normal and the patient to a state of well being over night Positive blood cultures often can be obtained before completion of the abortion and are the rule, if taken during the operation of curettage, according to Schottmuller, but most English and American authorities advise against curetting or any invasion of the uterine cavity except in the case of severe hemorrhage A positive blood culture after the uterus has been emptied usually indicates septicemia

While a single chill at the onset is common in all forms of postpartum infection the occurrence of repeated chills is strongly suggestive of septicemia although met with at times in localized infections showing negative blood cultures and progressing to early recovery The first indication of thrombophlebitis may be a sudden pain in the chest with or without a friction rub, the result of pulmonary embolism Enlargement of the spleen usually points to septicemia, although it is present occasionally in severe localized infections The distinction between the thrombophlebitic and the lymphangitic forms cannot always be made with certainty for chills often occur in the latter variety and the thrombosed veins in the broad ligament are not often palpable The occurrence of embolism of phlebitis of the femoral or saphenous veins by extension and the palpation of a tender cord in the broad ligament render the diagnosis of thrombophlebitis probable Generalized infections with the anaerobic streptococcus are associated almost invariably with thrombophlebitis

The *prognosis* formerly was very bad with a mortality of from 60 to 80 per cent It has improved markedly following the introduction of the sulfonamides and of penicillin

In *treatment* penicillin is to be preferred to the sulfonamides in infections with hemolytic streptococci staphylococci and *Cl welchii* Septicemia due to anaerobic streptococci should be treated with penicillin because this organism is resistant to sulfonamides

Surgical treatment is needed for pelvic abscesses but radical measures such as hysterectomy and excision of pelvic veins now are rarely indicated

SEPTIC ENDOCARDITIS

Acute endocarditis is described elsewhere in this system but since its occurrence during the course of septicemia constitutes an important and ominous event a few words about it will not be out of place here By septic endocarditis is understood inflammation of the cardiac valves occurring as a result of septicemia Acute and subacute or chronic forms may be distinguished

Acute Septic Endocarditis

Synonyms — Malignant endocarditis acute ulcerative endocarditis

The first to demonstrate bacteria in the valves was a Norwegian Heiberg by name in 1869 while Weichselbaum was the first to cultivate them in 1887 Acute endocarditis occurs in about *one fourth of all cases of septicemia* The streptococcus is as a rule the most frequent etiological factor with the staphylococcus a close second and the pneumococcus in third place In the series of Schottmuller and Bingold[1] however the staphylococcus stands at the head of the list These 3 organisms together account for about 80 per cent of the acute cases Gonococcal endocarditis is far less common except in the series of Thayer[164] in which owing to a large proportion of negroes this form constituted 14 per cent of the total The colon bacillus and the influenza bacillus occasionally are the cause and any of the other organisms met with in septicemia may at times produce endocarditis meningococcus pyocyaneus etc The left side of the heart was involved alone in 70 per cent, the right side in 15 per cent and both sides in 15 per cent according to Thayer s figures The mitral valve was affected somewhat oftener than the aortic except in the pneumococcic and gonococcic forms in which there was a strong preference for the aortic valve Thayer found the tricuspid valve involved either alone or with other valves in no less than 23 per cent the pulmonary valve in 9 per cent in gonorrheal endocarditis however the pulmonary valve was affected with striking frequency in 6 out of 21 cases 29 per cent

The statistics of Schottmuller and Bingold[12] based on 120 cases show a rather different distribution of the lesions They include cases of acute non rheumatic endocarditis and of subacute bacterial endocarditis in about equal proportions They found the mitral valve involved alone in 44 per cent the aortic valve in 9 per cent both the mitral and aortic in 28 per cent the tricuspid in 11 per cent the mitral and tricuspid in 1 7 per cent the mitral aortic and tricuspid in 3 5 per cent the pulmonary valve in 1 7 per cent the papillary muscles or trabeculae in 2 5 per cent

Usually it is stated that old valvular lesions predispose to septic endocarditis This is notably true in acute endocarditis due to the streptococcus in which Thayer found preexisting disease of the affected valves in 70 per cent It is less apparent in the case of the staphylococcus and the pneumococcus with 41 and 32 per cent respectively and with the gonococcus previous valvular disease was unusual being noted in only 4 per cent The nature of the preexisting disease was almost invariably rheumatic rarely syphilitic However it happens occasionally that patients with old valvular heart disease die of septicemia without developing fresh endocarditis and in other cases the acute vegetations are situated on one of the healthy valves not on the one previously diseased

The most common lesions are large polypoid vegetations, next in order of frequency comes ulceration of the valve covered with a thin layer of exudate and lastly small gray or reddish, verrucous lesions, which are of no clinical significance The destruction of the valve may be very slight or extensive and give rise to perforation The excrescences are soft and usually interfere little with the functioning of the valves while marked ulceration leads to insufficiency

The clinical course of septicemia is not altered, as a rule, by this type of endocarditis except when the breaking off of larger fragments of the vegetations leads to the signs of embolism of the spleen kidneys or brain The pulse rate is not more rapid than in many cases without endocarditis Occasionally, however, the violent action of the heart is suggestive of endocardial mischief

In about 40 per cent no murmurs are audible In the remainder there is often only a soft mitral systolic murmur such as is common in the absence of endocarditis in all the acute infectious diseases In other cases the murmur is loud and harsh and alters its character under observation Aortic diastolic murmurs are not uncommon the forcible apex beat and collapsing pulse of chronic aortic regurgitation do not develop on account of the patient s feeble condition and early demise The signs of decompensation do not appear in the absence of serious chronic valvular heart disease

From the above statements it is clear that a positive diagnosis during life often is impossible In the minority of cases it may be made provided that antecedent valvular disease can be excluded on the basis of a harsh systolic murmur or a diastolic murmur of any sort The diagnosis is particularly sure when the murmur first appears or alters its character under observation The occurrence of large emboli is very much in favor of septic endocarditis as in a recent personal case of staphylococcus infection in which gangrene of a toe developed the clinical diagnosis of endocarditis being made and confirmed at autopsy in spite of the absence of a significant murmur Blood cultures are positive at all times and show many colonies This finding according to Schottmuller and Bingold[1] should suggest the diagnosis of endocarditis even in the absence of a cardiac murmur, provided that no other focus for the distribution of bacteria can be discovered

Prognosis — Formerly acute septic endocarditis was almost invariably fatal Recently however Keefer[165] reporting for the Committee on Chemotherapeutic and Other Agents at the meeting of the New England Heart Association November 20th 1944 submitted the following encouraging collective figures of apparent cures observed with intensive penicillin therapy hemolytic streptococcus 33 per cent pneumococcus 30 per cent staphylococcus 23 per cent

Treatment — Penicillin is indicated in large doses as described in the following section on subacute bacterial endocarditis In the case of the staphylococcus larger doses are desirable 500 000 units or more daily

SEPTIC ENDOCARDITIS

Subacute Bacterial Endocarditis

Synonyms — Chronic infectious endocarditis subacute septic endocarditis endocarditis lenta

This form of endocarditis runs a protracted and characteristic course It was well described as long ago as 1881 by Litten[166] the discoverer of embolic retinal hemorrhages Osler[167] made notable contributions to the subject, while Schottmuller[168] and soon after him Libman[169] worked out the bacteriology Blumer's[170] excellent critical review in 1923 covers the field in a comprehensive manner and little has been added to our knowledge of the disease since that time The clinical picture is so manifold that it will be impossible to describe it completely in a short space and for fuller details the reader is referred to the above articles and to Chapter X–A in Volume II of Oxford Medicine

Subacute endocarditis is due in the great majority of instances to *Streptococcus viridans* Occasionally it is the result of infection with the staphylococcus endocarditis caused by the influenza bacillus usually runs a subacute course but owing to its rarity forms only a small proportion of the total The mitral valve is the one most often involved Previous rheumatic damage of the valves is found in about 80 per cent of the viridans cases Congenital heart disease also is a predisposing factor especially septal defects pulmonary stenosis and open ductus arteriosus Lewis and Grant[171] found bicuspid aortic valves, a congenital malformation in a high proportion of their cases 26 per cent In addition to the chronic lesions large polypoid vegetations are found on the valves and often on the wall of the left auricle These auricular vegetations are quite unusual in other forms of septic endocarditis their location possibly may be explained by the fact that according to Thayer mural lesions in the same region occur quite frequently in rheumatic endocarditis Here as in the case of the valves previous rheumatic inflammation prepares the ground for a later infection with *Streptococcus viridans* The chordae tendineae often are involved and may be ruptured The peripheral and visceral arteries frequently are the site of small aneurysmal dilatations the result of embolic arteritis sometimes these become large enough to be palpated and rupture may take place Characteristic embolic lesions of the glomeruli of the kidneys have been described by Lohlein[172] but Christian[173] has shown that the glomerular lesions are various and resemble those found usually in cases of acute Bright s disease

In accordance with the usual habitat of the viridans organism infection takes place mostly from the teeth or tonsils We have been struck by the frequency with which peridental abscesses are the source of the trouble In 2 personal cases the infection followed immediately on the extraction of abscessed teeth and in a third alveolar abscess necessitating extraction occurred very shortly after the first symptoms

The duration varies from a few months to a year or more During the greater part of this time the patient is able to be up and about The symptoms are extremely various Usually there is a fever of a low grade, intermittent or more often remittent Periods of apyrexia are not uncommon High intermittent fever with chills often indicates the detachment of emboli Multiple arthritis of a low grade and arthralgia are common Clubbing of the fingers often develops Signs of cardiac decompensation are not unusual towards the end Pericarditis and meningitis are rare complications Optic neuritis may be present The spleen almost always is considerably enlarged and firm Anemia of the secondary type is to be expected Leucocytosis often is absent and occurs chiefly during exacerbations Rarely the presence of macrophages in abundance gives the blood smear an extraordinary appearance

Embolic phenomena are observed very frequently and help to differentiate subacute bacterial endocarditis from other long continued fevers In many instances they constitute the most important single diagnostic sign They include hematuria either gross or microscopic as an indication of renal embolism pain and tenderness over the spleen, when that organ is infarcted hemiplegia, occasionally meningitic signs or headache and delirium in the case of cerebral embolism Sometimes sudden pain and coldness in an extremity with loss of pulsation occur as a sign that one of the main arteries to a limb has become plugged Petechial hemorrhages in the skin, the palpebral conjunctiva or the mucous membrane of the mouth almost invariably are met with at some time during the course of the disease Retinal hemorrhages are common Osler[167] has called attention to a very valuable diagnostic sign seldom met with in other conditions, the tips of the fingers or toes become painful very tender and show a purplish discoloration pea sized or somewhat larger These spots last a day or two and reappear from time to time Blumer[170] found them in 40 per cent of his cases

The *diagnosis* depends upon the demonstration of an old valvular lesion on the embolic phenomena the painful nodes, the clubbing of the fingers the petechiae and retinal hemorrhages A marked enlargement of the spleen is valuable confirmatory evidence The demonstration of bacteria in the blood usually *Streptococcus viridans* completes the diagnosis If the disease is borne in mind and the above points looked for, the diagnosis seldom is a difficult matter

Prognosis — The mortality of subacute bacterial endocarditis formerly was about 95 per cent With the intensive use of penicillin a death rate of 5 per cent or less may be expected The prognosis in general is better with early treatment but also depends on the condition of the patient and the sensitivity of the organism Severe congestive failure and extensive damage of the heart valves are unfavorable factors

Treatment — The sulfonamides will cause a temporary improvement which ceases soon after the drug is discontinued Penicillin in the early days when

the dosage was insufficient sometimes was effective but then relapses were the rule

The pioneer work of Loewe and his associates[173] however showed that penicillin given intravenously in large doses is very potent They reported 7 cases with return to health in all of them Five were due to *Streptococcus viridans* one each to hemolytic streptococcus and pneumococcus Penicillin was given by the drip method in doses up to 200 000 units daily over a period of 2 to 4 weeks Three cases relapsed and required more than one course of treatment They employed heparin as an adjunct in doses of 300 mgm every second day injected subcutaneously in a special menstruum

In a later publication Loewe[174] reported results with penicillin heparin therapy in 54 unselected consecutive cases A satisfactory outcome was obtained in 74 per cent Fourteen cases were failures He now advises a standard duration of treatment of 5 weeks with a dosage sufficient to maintain a penicillin level in the blood 5 to 10 times greater than the sensitivity of the infecting strain Usually a daily dose of 200 000 units is sufficient but in refractory cases he employed up to one million units

Dawson and Hunter[175] using Loewe s technic published 16 cases with recovery in 75 per cent In an addendum they mention 7 additional cases treated with the intramuscular drip method as described by Harris[176] In 5 of these penicillin was used alone i e without heparin The results were satisfactory in 6 the remaining case was being treated for a relapse at the time of writing They found higher and more constant levels with the intramuscular drip than with the intravenous method and consider that the method of choice

Meads Harris and Finland[177] observed 9 cases due to *Streptococcus viridans* treated for the most part with intermittent intramuscular injection The result was satisfactory in 7

Coerner Geiger and Blake[178] report 12 cases of viridans endocarditis treated with penicillin without heparin with apparent cure in 11 92 per cent Their cases were unselected with the exception that 2 patients admitted in a moribund condition at a time when penicillin was scarce were not treated They used the intravenous drip method in doses of 240 000 to 600 000 units daily over a minimum period of 3 or 4 weeks The majority of patients responded well to 240 000 units daily while 2 cases that relapsed required 400 000 units There was an unusually high proportion of females in this series 11 out of 12 The single failure was a case with a rather high sensitivity figure 0 05 units the bacteriemia was controlled in each of 4 courses totalling 33 million unit but recurred as soon as treatment was discontinued and the patient died

From the reports in the literature it may be concluded that recovery is to be expected in 75 per cent or more While it would not be surprising if some of these patients suffered a reinfection at a future date many of them have remained well

for a year or more while the remainder have been followed for shorter periods Under these circumstances it seems permissible to speak of a cure

The rapid improvement of these patients is truly surprising Bacteriemia ceases after a few days, the temperature returns to normal or nearly so and there is a prompt gain in weight and in general condition

Summary of treatment — At the present time the method of choice is continuous intravenous administration of penicillin A further trial of the intramuscular drip method of Harris[176] is desirable Intermittent intramuscular injections are less reliable and should be used only as a temporary expedient, when the intravenous drip is not feasible Penicillin should be given in amounts of 240 000 to 500 000 units daily and in rare instances even more may be required If relapse occurs, an increase in the dose usually is indicated The dosage is controlled by the penicillin levels in the blood which should be 5 to 10 times the sensitivity of the organism

The usual duration of a single course of treatment is 3 to 5 weeks Relapses have been less frequent since the procedure has been improved but in some instances as many as 4 courses have been needed An increase in resistance to penicillin of the infecting strain during treatment occasionally has been noted in one case up to forty fold (Loewe)

The use of heparin does not seem necessary for equally good results have been obtained with penicillin alone, and heparin often causes fever and sometimes hemorrhage

In the presence of severe congestive failure it is better to restrict the fluid intake and give penicillin by intermittent intramuscular injection After cardiac failure has been controlled by digitalis the intravenous drip may be started

During convalescence prolonged rest in bed is important Frequent blood cultures should be taken and a return of bacteriemia calls for an increase in the dose or resumption of treatment if it has been stopped Occasionally a latent rheumatic fever becomes active and can be controlled by salicylates To prevent reinfection diseased teeth or tonsils should be removed after an interval of several months This can be accomplished safely, if penicillin is given for three days starting the day before operation An appropriate dose is 10 000 to 20 000 units every 3 hours by the intramuscular route

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CHAPTER XXX-A

THE SULFONAMIDE COMPOUNDS IN THE TREATMENT OF INFECTIONS

By MAURICE A. SCHNITKER

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PART I

INTRODUCTION

In the first three decades of this century the major avenue of progress in scientific medicine has been made through careful study of infecting agents and the reactions caused by them in human tissues. In this avenue of approach namely bacteriology and pathology tremendous strides have been made and will continue to be made. *However as in any scientific* endeavor here too the study of gross and microscopical alterations of structure has not satisfied entirely the inquiring mind and as a result during the last ten years the newer and more revealing approach has been in the field of chemistry. Whereas pathology has taught us the alterations of structure that can occur with disease now chemistry is revealing the explanations for disturbances of function in disease. Not that chemistry is taking up where pathology left off for they are intimately interrelated but the chemical approach to the subject of human disease has led to new trends of thought and new channels of approach and it has traveled with seven league boots in the last decade.

Perhaps the outstanding example of chemical progress in medicine is the discovery and widespread use of the sulfonamide compounds in the field of therapy of infections. Bordering on the miraculous as the progress has been in this field it has not been uniform entirely for clinical application of these drugs life saving as they have proved to be has lagged behind test tube knowledge of them. Since the introduction of prontosil by Gerhardt Domagk in February 1935[1] for the treatment of streptococcal infections the frenzied research of the past seven years has resulted in the synthesis and disclosure of about 1 300 new compounds derived from the parent molecule of sulfanilamide. Northey has estimated that when allied compounds and undisclosed sulfanilamide derivatives are added to these it is probable that more than 3 000 new compounds are available for chemotherapeutic study. Many of these were found quickly to be entirely unsuitable for animal or human benefit but such figures will demonstrate amply the vast and unpredictable possibilities that lie in the future.

Although the chemist seems far ahead of the pharmacologist the animal experimentalist and finally the clinician in the subject of the sulfonamide drugs no voice should be raised in criticism for these three working together must labor long and untiringly in *making these drugs* effective and yet safe for human consumption. To the time of this writing

5 of the 3 000 chemicals have been demonstrated to be effective in certain infections and not very harmful to the tissues of the host and have been utilized successfully in the treatment of certain human diseases Known upon the American market as sulfanilamide sulfapyridine sulfathiazole sulfadiazine and sulfaguanidine these 5 drugs will constitute the major discussion of this chapter Certain of the related compounds that have been introduced and later more or less discarded because of their toxic effects upon the host will be considered briefly also in connection with certain diseases

This chapter will attempt to bring up to date the knowledge concerning the newer preparations that have been introduced during the past two years as well as to present modifications of thought and new trends in the earlier concepts of the parent drugs sulfanilamide and sulfapyridine It is appreciated that the discovery of the therapeutic action of the sulfonamide drugs was and continues to be made in the laboratory by experiments on small animals yet it is realized that much of the detailed information so acquired has not been applied yet to human beings However, enough has been learned by their use in human patients so that the major portion of the following discussion will be based upon the actions and effects of these drugs in the human organism

The history pharmacology and the mode of action will be considered under the respective headings for the drugs as a group Each drug will be considered separately with reference to the methods of administration and dosage and to the particular diseases in which it has proved to be most effective It will be attempted to stress the specific drug for the specific infection for it appears that one of the chief problems which confronts the clinician today is the selection of the proper drug for the treatment of a particular infection in other words when to use which drug where It is felt that it has not been appreciated sufficiently that the sulfonamide derivatives differ from compound to compound not only in their scope and effectiveness of therapeutic activity but also in their pharmacological properties The toxic effects will be considered in the discussion of each individual drug

Because of the enormous duplication of experimental and clinical results a complete bibliography would consume a great many pages and would not be of particular interest in connection with this discussion Much of the information has become common knowledge for which the writer will assume the responsibility but credit for the basic principles and the major advances have been given appropriate recognition in the bibliography at the end of the chapter

History of Sulfonamide Chemotherapy

Chemotherapy in the strictest sense of the word may be considered to be of comparatively ancient origin In the case of protozoan infections the use of mercury in syphilis in the 16th century the use of cinchona bark in remittent fevers in the 17th century and the application of ipecac in dysentery may be spoken of as almost specific forms of chemotherapy[3]

Since the latter part of the 19th century when it was discovered that bacteria were the causes of many of the diseases of mankind it has been a desideratum in medicine to cure such diseases by the introduction of chemicals into the body to destroy the bacteria In the first third of this century perhaps only two attempts along this line have been successful Ehrlich s introduction of salvarsan[4] in 1904 was epoch making and has stood the test of time but only after he had tried six hundred and five preparations that were unsuccessful His efforts demonstrated clearly the difficulties of chemotherapy From time to time attempts have been made to cure bacterial infections in animals by the use of chemical drugs but these all met with little or no success with the exception of the discovery of Morgenroth and Levy in 1911[5] that ethylhydrocuprein would cure mice of a pneumococcus infection but this has had only limited clinical application

Beyond doubt the greatest contribution to chemotherapy yet made was the introduction of the substance called prontosil by Gerhardt Domagk in February 1935 who showed that this sulfonamide compound was effective in preventing death in experimental streptococcal infections in mice Like many great medical discoveries it did not spring suddenly over the horizon but was the result of much painstaking thought and labor To most of us it was new and its application to the treatment of disease was new but to the chemical industry the sulfonamide compounds had been known and used for many years In this industry Horlein Dressel and Kothe[6] prepared some of the first azo dyestuffs with sulfonamide and substituted sulfonamide groups in 1909 Among the azo dyes chrysoidin (2 4 -diaminoazobenzene) and its related derivatives have been used in the textile industry for over thirty years to color cotton wool and silk various shades of red orange or yellow During the investigations of the action of these dyestuffs on wool it was noted that the sulfonamide preparations in their staining qualities formed a more intimate combination with the protein of the cells than did the azo dyes which lacked the sulfonamide group This fact stimulated Eisenberg in 1913[7] to study the effects of these dyes on the behavior of

bacteria and their proteins which led to his discovery that they possessed a relatively strong bactericidal action in vitro Eisenberg introduced chrysoidin as a chemotherapeutic agent and at one time this drug was used in the treatment of trypanosomiasis Subsequently various azo compounds as pyridium mallophene and serenium were introduced into medicine chiefly as urinary disinfectants but with therapeutic results that were not entirely satisfactory

In 1932 in further study of the azo compounds Mietsch and Klarer[8] in the laboratories of the German I G Farbenindustrie synthesized a hydrochloride of 4 sulphamido 2 4 diaminoazobenzene a red crystalline powder with melting point 247°–251° C and soluble in cold water to 0 25 per cent It was this substance that was shown by Domagk in 1935 to exert a protective action when given intravenously to mice infected with streptococci This chemical a derivative of chrysoidin he termed prontosil The first clinical report on the use of sulfonamido-chrysoidine prontosil was by Foerster in 1933[9] in a case of widespread staphylococcal infection The dihydrochloride prontosil flavum and the disodium salt neoprontosil soon made their appearance and were utilized

In confirming Domagk s work there followed very quickly one of the most important of contributions that of Trefouel Trefouel Nitti and Bovet[10] Recalling the hypothesis advanced by Heidelberger and Jacobs in 1919[11] concerning the chemistry of sulfonamide compounds their cleavage and breakdown they postulated that sulfonamido chrysoidine was broken down in the tissues at the azo linkage to triaminobenzene and para aminobenzene sulfonamide the latter of which they assumed to be the effective pharmacological portion of the prontosil molecule This finding was confirmed entirely by Colebrook Buttle and O Meara[12] and Fuller[13] in England and by Long and Bliss[14] in this country The importance of this finding may be emphasized by the fact that several thousand related compounds have been synthesized and tested since then and only a few with the basic sulfanilamide molecule have shown the chemotherapeutic activity of sulfanilamide in man When para aminobenzene sulfonamide sulfanilamide was found to be the effective agent a quick review of chemical history showed that it too was not a new substance for it had been synthesized by Gelmo in 1908[1] and it had been interred in Beilstein for over 30 years

This rapid succession of events has made it seem as if the first shot had struck the bull s eye and little further remained to be done in this direction These discoveries therefore seemed to bring the world for the first time within sight of an internal antiseptic that is one which

would control bacterial infection by way of the blood stream It surpasses Ehrlich s discoveries which were limited to the field of trypanosome diseases since it has led already to cures of most of the common infectious diseases of bacterial origin Rightly therefore Domagk was given the award of the Nobel Prize for Physiology and Medicine for 1939 an award unfortunately that the Nazi regime of Germany forbade him to accept

The introduction of prontosil and its related compounds prompted many experiments in infected rabbits guinea pigs mice cats and dogs all of which tolerated this substance well In the human patient the drugs were found quickly to be effective in numerous bacterial diseases not only streptococcic but gonococcic meningococcic etc In one prevalent and highly mortal condition namely pneumonia the results were discouraging Such a state always is a challenge to the medical scientist so it was to be expected that new chemicals would be sought for as an effective chemotherapeutic agent for the treatment of pneumococcus infections With some such point of view Buttle in 1937 reported that the benzylidene Schiff s base of diaminodiphenylsulfone was more effective than sulfanilamide in prolonging the life of mice infected with type I pneumococci This compound however was four times as toxic as sulfanilamide In the same year Whitby found two diaminobenzene sulfanilide compounds that were two to three times more efficient than sulfanilamide for type I pneumococci in mice but again toxic After persistent efforts in the spring of 1938 Whitby[16] introduced the second of our 5 compounds 2 (p-aminobenzene sulfonamide) pyridine or sulfapyridine which he found to be effective in the treatment of pneumococcic infections in mice as well as infections due to hemolytic streptococci meningococci and staphylococci

Very quickly sulfapyridine proved to be most effective in the treatment of pneumococcic infections in man particularly pneumococcus pneumonia With these observations it became apparent also that this new drug carried with it two distressing other effects namely nausea and vomiting This feature plus its lower solubility when compared with sulfanilamide and its erratic absorption and distribution in the body which is discussed under the pharmacology of these drugs led to the introduction of the sodium salt of sulfapyridine for intravenous use by Marshall and Long[17] in 1939

Continuation of the search for new drugs which would be more effective and at the same time less toxic to the host led to the synthesis of sulfathiazole and sulfamethylthiazole independently by Fosbinder and Walter[18] and by Lott and Bergeim[19] early in 1939 Particularly in regard

to pneumococcic infections to which it has been applied chiefly, sulfathiazole has proved to be just as effective as and less toxic than sulfapyridine with a less incidence of nausea and vomiting when given to patients with pneumonia Its sodium salt for intravenous administration soon appeared

In the same quest for new and more effective drugs sulfadiazine made its appearance having been synthesized by Roblin Williams Winnek and English in 1940[70] In further experiments it was found that sulfadiazine caused less tissue damage and yielded higher blood concentrations than either sulfapyridine or sulfathiazole and that it had a high therapeutic activity against pneumococcal streptococcal staphylococcal and group B Friedlander bacillus infections[1]

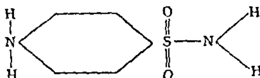
During a similar comprehensive study of various sulfonamide derivatives Marshall encountered several water soluble compounds which were poorly absorbed from the gastrointestinal tract One of these sulfanilyl guanidine sulfaguanidine he presented in 1940[illegible] as a possibly effective compound for the treatment of certain intestinal infections with bacteria mainly in the intestinal canal thus introducing a new principle in the use of bacterial chemotherapeutic agents

As these newer and often more effective drugs were being introduced the original parent substance sulfanilamide unfortunately and often unnecessarily became neglected by many clinicians in their practise Then as sulfapyridine and sulfathiazole were replacing sulfanilamide almost completely and often undeservedly Jensen Johnsrud and Nelson[23] in 1939 introduced the local application of sulfanilamide Since sulfanilamide seems to be the most effective drug for local use with the most widespread application in this field it again emphasizes the fact that all of these drugs are extremely useful no one to the exclusion of the others indicating that a specific drug is to be chosen for a particular situation

Up to the time of this writing all 5 of the drugs have been released for clinical use by the Federal Food and Drug Administration but only 3 sulfanilamide sulfapyridine and sulfathiazole have been accepted by the Council on Pharmacy and Chemistry of the American Medical Association

CHEMISTRY OF SULFONAMIDES

Sulfanilamide Known chemically as para aminobenzene sulfonamide is the amide of sulfanilic acid and has the structural formula



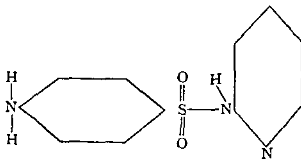
It occurs as a white practically odorless crystalline substance slightly bitter with sweet after taste It is soluble in hot water hot alcohol and cold acetone slightly soluble in cold water (0 8–1 0 per cent) and cold alcohol and insoluble in ether benzene and chloroform In an aqueous solution it is neutral to litmus Sulfanilamide is an amphoteric substance forming salts with both strong acids and bases The salts formed from bases hydrolyze in water to give pH values of 10 to 11 while the salts with acids give values of pH 2 to 3 The melting point is 165°–167° C Crystallographic analysis of sulfanilamide has shown an index of refraction of approximately 1 6 Given the trade name of sulfanilamide by the Council of Pharmacy and Chemistry of the American Medical Association [4] it is marketed in powder and tablet form In England and on the European continent it also bears such names as ambesid astreptine colsulanyde deseptyl ergaseptine erysipan gombardol lysococcine neococcyl orgaseptine prontosil album prontylin proseptine proseptol pysoccine rubiazol A septamide septoplix stopton album stramid streptazol streptocide streptoclase streptozone sulfamidyl sulfina sulfanil p sulphamido aniline sulphonamide P supron and therapol

In a consideration of the chemistry of the derivatives of sulfanilamide which are useful clinically it is of interest to note that these related compounds follow distinct chemical and pharmacal laws which are not completely understood biologically The first fact is that in all of the active compounds the effective nitrogen nitro amino or substituted amino group is in the para position in the benzene ring The sulfonamides are not unique in this respect for in such chemical substances as dinitrophenol thyroxin epinephrine and ephedrine all of which are active in the human body the effective nitrogen is in the para position Others have regarded sulfur as an indispensable part of the molecule the para linkage of the sulfur being an important feature Parenthetically however it always has been an interesting fact that the pharmacological action of a drug cannot be predicted regularly on the basis of chemical structure In the isomers of sulfanilamide shifting the amino group to the ortho or meta position in the benzene ring results in almost inactivity Replacing the amino group in the benzene ring with –H –OH –OR –COOH SO_2NH_2 an alkyl or a halogen practically destroys the activity Re

placing the sulfonamide group of the ring by $-NH$ $-CN$ $-SO_3H$, $-AsO_3H$ $-CONH_2$ $-NHCOCH_3$ and $-NO_2$ also destroys the activity but replacement of the sulfonamide group by $-SO\ H$ retains most of the activity In nuclear substituted sulfanilamides the introduction of a halogen amino sulfonamido methyl or carboxyl group into the sulfanilamide ring also destroys the activity

Thus with these pharmacological limitations of the chemical derivates of sulfanilamide careful analysis of the active compounds related to the parent substance sulfanilamide shows that they may be divided into two classes The *first group* which includes the original prontosil of Domagk consists of those derivatives in which substitutions have been made in the para amino group These include such substances as prontosil the more soluble neoprontosil and N^4 benzylsulfanilamide septazine which probably break down in the body to form sulfanilamide The *second group* consists of those derivatives in which the substitutions are in the sulfonamide group at the other end of the benzene ring leaving the para amino group free Among these are included sulfanilyl sulfanilamide and its dimethyl derivative diamino diphenyl sulfone sulfapyridine sulfathiazole sulfamethylthiazole and sulfadiazene Many derivatives of the second class are not decomposed to any appreciable extent in the human organism and owe their activity apparently to the molecule as such Further studies that are being carried out suggest at least that the road to further improvement both in scope and effectiveness of action may lie in the second group i e in substitutions in the sulfonamide group

The first successful sulfonamide substitution was accomplished in *sulfapyridine* known chemically as 2 (p aminobenzene sulfonamide) pyridine It was introduced first as M and B 693 product number 693 of the May and Baker Chemical Company and was known also as dagenan a variant of Dagenham the site of the May and Baker factory In certain localities in Europe it is also known as ronin The chemical formula i

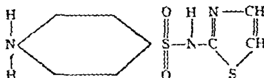


The non proprietary name sulfapyridine has been adopted for this substance by the Council on Pharmacy and Chemistry of the American Medical Association This compound is a white crystalline almost tasteless solid soluble in water at ordinary temperatures to the extent of approximately 1 in 1 000 thus only about one tenth as soluble as sulfanilamide *From the constitutional formula it will be seen that the* compound differs from sulfanilamide in that one hydrogen of the $-SO_2NH_2$ group is replaced by a basic pyridine group The melting point is *19 ± 1 C It is soluble to the extent of about 0 25 per cent in 95* per cent alcohol and soluble in acetone It forms water soluble salts with strong bases and mineral acids the basic salt having a pH of 10–11 *the acid salt a pH of 2–3 It is supplied in tablet and powder form*

Sodium sulfapyridine the basic salt is a white odorless practically tasteless crystalline powder highly soluble in water up to 75 gm in 100 c c The resulting solution is very alkaline pH 10 4 to 11 0 It is unstable to heat and hence such solutions cannot be sterilized Potentiometric titration of the salt shows that precipitation occurs after a slight decrease of pH and is complete for this compound at pH 9 0 Introduced originally for intravenous use only it has been utilized also subcutaneously intramuscularly orally and rectally This will be discussed under the heading of dosage and administration of sulfapyridine

Glucose sulfapyridine is a combined form of glucose and sulfapyridine introduced and tried by several investigators for the treatment of pneumococcic pneumonia

Sulfathiazole the second successful sulfonamide substitution product of sulfanilamide is known chemically as 2 para aminobenzene sulfonamide thiazole or 2 sulfanilyl aminothiazole It is a white crystalline powder practically odorless and tasteless Its structural formula is

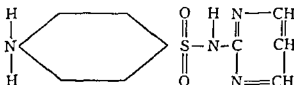


It is poorly soluble in cold water and at 78 C 90 mgm will go into *solution in 100 c c and 600 mgm in 1 000 c c of water It is soluble in glacial acetic acid and in pyridine slightly soluble in ethyl methyl* and isopropyl alcohols and insoluble in benzene chloroform ether ethyl acetate and ethylene dichloride It is soluble in dilute mineral acid *solutions and alkali metal hydroxide and carbonate solutions Sulfathia*zole melts at from 200 –203 5 C with slight decomposition When the

melting point is determined using a micromelting point stage there may be indicated the presence of two crystalline forms having separate melting points Crystals melting at about 172°–173° C may be observed to undergo a transition into the solid state at this temperature and if remelted may recrystallize in a form having a melting point of 200°–203 5° C Further observations will be required to determine whether these two substances induce a difference in pharmacological activity and in toxicity Known on the European continent also by the name M and B 760 May and Baker Co product number 760 it has been given the name sulfathiazole It is supplied in powder and tablet form

The sodium salt of sulfathiazole has been prepared for intravenous use and subcutaneous administration It has an optimum solubility of 5 per cent in water but is stable up to 20 per cent It too is alkaline but despite the fact that it contains essentially the same amount of sodium as sodium sulfapyridine sodium sulfathiazole in the same concentration has a pH of 9 4 Potentiometric titration of sodium sulfathiazole and sodium methylthiazole shows that precipitation occurs with a decrease of pH to 7 0

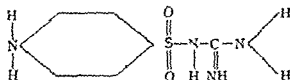
Sulfadiazine the third successful substituted sulfonamide is known chemically as 2 sulfanilamidopyrimidine It has the following structural formula



Synthesized by Roblin Williams and Winnek these authors felt that if given the name sulfapyrimidine it was certain to cause confusion with sulfapyridine and since pyrimidine is a diazine ring they suggested the name sulfadiazine It is a white odorless crystalline powder prepared by condensing 2 amino pyrimidine with acetyl sulfanilyl chloride and subsequent hydrolysis It is sparingly soluble in water 0 0123 gm per 100 c c and insoluble in ether and chloroform Sulfadiazine is unstable in boiling water on autoclaving *in aqueous solution* and in sunlight It is readily soluble in alkalies and mineral acids The melting point is 253°–256° C The crystals of sulfadiazine take the form of long thin needles when precipitated from water and in the urine they have been described as resembling sheaves of wheat or bundles of long needles It may be determined quantitatively by titration with $\frac{1}{10}$N sodium nitrite using starch potassium iodide as an outside indicator

Sulfaguanidine is one of a series of compounds a sulfonamide deriva

tive introduced by Marshall Chemically it is known as sulfanilyl guanidine and it has the following structural formula



It is a white odorless practically tasteless crystalline powder prepared by condensing acetylsulfanilylchloride with guanidine nitrate and subsequent hydrolysis It is sparingly soluble in water 0 22 gm per 100 c c and is insoluble in benzene ether and chloroform It is readily soluble in cold mineral acids but insoluble in cold alkaline solutions In comparing these compounds in water at 37 5° C sulfaguanidine is soluble to 220 mgm per cent sulfanilamide to 1 480 mgm per cent sulfapyridine to 54 mgm per cent and sulfathiazole to 96 mgm per cent The melting point of sulfaguanidine is 189°–190° C but it melts in a sealed tube at 143–144° C It may be determined by titration with $\frac{1}{10}$N sodium nitrite using starch potassium iodide as an outside indicator

Assay of Sulfonamide Compounds in Blood Urine Feces and Body Tissues and Fluids

The method of assay of sulfanilamide and related substances in the blood urine feces body fluids and tissues has been developed by Marshall[7 28 29] and others and is simple enough for routine clinical use The method after deproteinization of the blood or urine is based on the diazotization of para aminobenzene sulfonamide with nitrous acid and the coupling of the resulting diazo compound in acid solution with a naphthylamine The reaction results in a purplish red azo dye which can be estimated colorimetrically The color reaction is very delicate permitting the detection of one part of sulfanilamide in 20 million parts of water

Solutions required

1 Trichloracetic acid 15 gm dissolved in water and diluted to 100 c c
2 Sodium nitrite 0 1 per cent solution
3 N(1 naphthyl) ethylenediamine dihydrochloride a solution containing 100 mgm in 100 c c water Keep in dark colored bottle
4 Saponin 0 5 gm per liter
5 Hydrochloric acid 4N

6 Ammonium sulfamate 0 5 gm per 100 c c water

7 Stock solution Sulfanilamide in water 200 mgm per liter Weigh out the correct amount of sulfanilamide crystals and dissolve in hot water Dilute to 1 000 c c This solution can be kept for several months in the icebox Prepare standard as required from this stock The usual standards are 1 0 0 5 and 0 2 mgm per 100 c c To prepare these add 5 2 5 and 1 c c of the stock 18 c c of the 15 per cent trichloracetic acid and dilute to 100 c c

PROCEDURE BLOOD (*Macromethod*) — *Free Sulfonamide* — Pipette c c of oxalated blood into a flask containing 30 c c of saponin solution and mix the contents well After one or two minutes precipitate the protein with 8 c c trichloracetic acid Mix thoroughly and after five minutes filter To estimate the amount of sulfonamide drug present add 1 c c of the sodium nitrite solution to 10 c c of this filtrate Let stand three minutes and add 1 c c of the sulfamate solution After two minutes add 1 c c of the N(1 naphthyl) ethlenediamine dihydrochloride solution Compare the color developed with that of a standard treated in exactly the same manner There will be no change in color for an hour or more

The above method is applicable for the determination of any one of the five sulfonamide compounds under discussion However in carrying out comparative studies with the old and the new coupling reagents with the above drugs (courtesy Miss G Kazmaier) it was found that frequently the newer coupling substance N(1 naphthyl) ethylenediamine dihydrochloride (the one used here) gives a higher reading in the case of sulfapyridine than the actual content in the blood It has been our experience that for sulfapyridine determinations of the blood the original coupling reagent N N dimethyl 1 naphthylamine (dimethyl a naphthyl amine) has given the more accurate figure when tested by the addition of a given quantity of sulfapyridine to a given quantity of blood Similarly we have found that if the original reagent dimethyl a naphthylamine is used in the determination of sulfadiazine the reading may be too high The newer coupling compound is to be preferred in the determination of sulfanilamide sulfathiazole and sulfadiazine

Total Sulfonamide in Blood — This consists in the determination of the conjugated acetyl sulfonamide compound For total sulfonamide treat 10 c c of the filtrate with 0 5 c c 4N hydrochloric acid Heat in a boiling water bath for one hour cool and adjust the volume to 10 c c The remainder of the procedure is the same as for free sulfonamide

URINE (*Macromethod*) — Dilute urine specimen until there is between 1 and 2 mgm per cent concentration of sulfanilamide This may be e ti

nated by the knowledge that generally after balance has been reached in the body one gram of sulfanilamide per day will give a concentration of 100 mgm per cent in the urine of which half will be free and half conjugated To 50 c c of the diluted urine add 5 c c of 4N hydrochloric acid and dilute to 100 c c Using 10 c c samples of the diluted acidified urine carry out the same procedure as outlined under blood for sulfanilamide and derivatives Calculation is the same as under blood The dilution factor D varies as the dilution required to reduce the sample to 1 2 mgm per cent

Calculation Set standard cup in Dubosq type of colorimeter at 20 mm

$$\frac{20}{R} \times S \times D = \text{mgm per cent}$$

R = Reading of unknown solution
S = Standard taken
 a where 1 0 mgm per cent is standard S equals 1 0
 b where 0 5 mgm per cent is standard S equal 0 5
 c where 0 2 mgm per cent is standard S equals 0 2
D = Dilution taken
 a if 1 10 D equals 10
 b if 1 20 D equals 20 etc

When the 1 20 dilution as outlined above is used any value over 5 mgm per cent should be increased by 10 per cent If the value is less than 5 mgm per cent no correction is required

With the use of a *photoelectric colorimeter* for the macro determination of these drugs various standards are supplied with the individual machines With such a colorimeter a *filter* is essential In the case of dimethyl a naphthylamine used as the coupling reagent the peak of absorption of the azo dye formed occurs at 530 mu For N(1 naphthyl) ethylenediamine dihydrochloride the peak of absorption occurs at 545 mu

BLOOD (*Micromethod*) — A micromethod requiring only 0 1 c c of capillary blood the determination being carried out with a photoelectric colorimeter has been described by MacLachlan Carey and Butler[39]

Take 0 1 c c of capillary blood by finger prick in a pipette calibrated to contain 0 1 c c. Deliver this to a centrifuge tube containing 1 c c of 0 05 per cent solution of saponin and rinse the pipette by drawing this solution up to the calibration mark several times Let stand for five minutes then add to it 3 c c of 5 per cent p toluenesulfonic acid solution Unless the conjugated form of sulfanilamide is to be determined a 5 per cent solution of trichloracetic acid may be substituted for the

6 Ammonium sulfamate 0 5 gm per 100 c c water

7 Stock solution Sulfanilamide in water 200 mgm per liter Weigh out the correct amount of sulfanilamide crystals and dissolve in hot water Dilute to 1 000 c c This solution can be kept for several months in the icebox Prepare standard as required from this stock The usual standards are 1 0 0 5 and 0 2 mgm per 100 c c To prepare these add 5 2 5 and 1 c c of the stock 18 c c of the 15 per cent trichloracetic acid and dilute to 100 c c

PROCEDURE BLOOD (*Macromethod*) — *Free Sulfonamide* — Pipette 2 c c of oxalated blood into a flask containing 30 c c of saponin solution and mix the contents well After one or two minutes precipitate the protein with 8 c c trichloracetic acid Mix thoroughly and after five minutes filter To estimate the amount of sulfonamide drug present add 1 c c of the sodium nitrite solution to 10 c c of this filtrate Let stand three minutes and add 1 c c of the sulfamate solution After two minutes add 1 c c of the N(1 naphthyl) ethlenediamine dihydrochloride solution Compare the color developed with that of a standard treated in exactly the same manner There will be no change in color for an hour or more

The above method is applicable for the determination of any one of the five sulfonamide compounds under discussion However in carrying out comparative studies with the old and the new coupling reagents with the above drugs (courtesy Miss G Kazmaier) it was found that frequently the newer coupling substance N(1 naphthyl) ethylenediamine dihydrochloride (the one used here) gives a higher reading in the case of sulfapyridine than the actual content in the blood It has been our experience that for sulfapyridine determinations of the blood the original coupling reagent N N dimethyl 1 naphthylamine (dimethyl a naphthyl amine) has given the more accurate figure when tested by the addition of a given quantity of sulfapyridine to a given quantity of blood Similarly we have found that if the original reagent dimethyl a naphthylamine is used in the determination of sulfadiazine the reading may be too high The newer coupling compound is to be preferred in the determination of sulfanilamide sulfathiazole and sulfadiazine

Total Sulfonamide in Blood — This consists in the determination of the conjugated acetyl sulfonamide compound For total sulfonamide treat 10 c c of the filtrate with 0 5 c c 4N hydrochloric acid Heat in a boiling water bath for one hour cool and adjust the volume to 10 c c The remainder of the procedure is the same as for free sulfonamide

URINE (*Macromethod*) — Dilute urine specimen until there is between 1 and 2 mgm per cent concentration of sulfanilamide This may be esti

where V equals the galvanometer reading for that solution A equals the cubic centimeters of original blood or urine used in the analysis and K equals a constant for the particular colorimeter used The value for K for the Evelyn colorimeter used by these authors was 503±8 As a matter of convenience the concentration of acetyl sulfanilamide may be calculated as sulfanilamide Since the former yields 80.3 per cent of its weight as sulfanilamide sulfanilamide times 1.245 equals the acetyl compound

The micromethod may be used for the other sulfonamide compound and interpolation may be carried out by reference to the table of conversion factors

Because of the inconvenience required frequently particularly in the small laboratory of maintaining standard solutions of all the drugs a table of conversion factors can be derived based upon the anhydrous molecular weights of these various compounds The anhydrous molecular weights are as follows

Sulfanilamide	172
Sulfapyridine	249
Sulfathiazole	255
Sulfadiazine	250
Sulfaguanidine	214

For example if one is examining for sulfapyridine using a sulfanilamide standard one multiplies the colorimeter reading by 249/172 = 1.47 These conversion factors have been set up in table form for ready reference thus eliminating the trouble required to maintain corresponding standard solution This conversion table is enjoying wide use in hospital laboratories and is accurate to within ±5 per cent

TABLE I

TABLE OF CONVERSION FACTORS

Standard	Conversion Factor				
	Sulfan	Sulfap	Sulfath	Sulfad	Sulfag
Sulfanilamide		1.47	1.48	1.45	1.24
Sulfapyridine	0.69		1.0	1.00	0.86
Sulfathiazole	0.67	0.97		0.98	0.84
Sulfadiazine	0.68	1.00	0.69		0.85
Sulfaguanidine	0.80	1.16	1.19	1.17	

p toluenesulfonic acid Mix let stand five minutes filter Remove 2 cc and 1 cc of the filtrate to each of two colorimeter tubes for the determination respectively of the free and total sulfanilamide the tube to contain the latter being graduated at a volume of 10 cc Insert a cork with capillary opening into the tube for total sulfanilamide determination and place in a boiling water bath for ninety minutes Then add 1 cc water and cool

For the blank determination add to a colorimeter tube 0 5 cc of the saponin solution and 1 5 cc of the p toluenesulfonic acid solution

To each of the three colorimeter tubes two containing the samples of filtrate and one the blank sample add 4 5 cc of water and 0 5 cc of 0 1 per cent sodium nitrite solution Mix and let stand at room temperature for five minutes To each tube as near the same time as practical add 3 cc of 0 4 per cent dimethyl alpha naphthylamine alcohol solution (1 cc of dimethyl alpha naphthylamine in 250 cc of 95 per cent ethyl alcohol) After mixing the color usually develops in five minutes After this interval insert the tube containing the blank sample into the colorimeter and adjust the galvanometer reading to 100 Remove the tube containing the blank note the reading of the galvanometer with no tube in place This is the center setting Immediately insert one after the other the tubes containing the unknown samples and record the respective galvanometer readings Repeat after ten and twenty minutes to insure full color development

URINE (*Micromethod*) The procedure for urine (micromethod) is to dilute the urine so that the concentration of sulfanilamide is between 0 02 and 0 25 mgm per cent The required dilution can be estimated from the dosage of sulfanilamide and the urine volume To 5 cc of the diluted urine in a colorimeter tube add 1 5 cc of p toluenesulfonic acid reagent and 0 5 cc of sodium nitrite solution For the determination of total sulfanilamide the acidified urine is incubated before the addition of the nitrite solution and the total volume in the colorimeter tube adjusted to 10 cc after the addition of the dimethyl alpha naphthylamine solution as described in the micro procedure for whole blood After the addition of sodium nitrite mix and let stand five minutes Add 3 cc dimethyl alpha naphthylamine reagent Mix and after five minutes read the galvanometer deflection using the center setting from the blank tube as described in the procedure for whole blood

The milligrams of sulfanilamide per 100 cc of blood or original urine are obtained by the following equation

$$\text{mgm per cent} = \frac{100 \times V(2 - \log G)}{A \times K},$$

filtrate (equivalent to 1 c c of milk) plus 1 c c of 6N hydrochloric acid are put into a test tube 25 by 200 mm covered with a small beaker and placed into boiling water for thirty minutes After cooling one drop of phenolphthalein is added and the hydrolyzed mixture is neutralized with concentrated sodium hydroxide solution Transfer to a 10 c c volumetric flask and dilute to volume Five c c of this diluted material is pipetted into a 25 c c test tube and the analysis for sulfanilamide made To 5 c c of the filtrate are added 5 c c of water 2 c c of 0 1 N hydrochloric acid 5 c c of 95 per cent ethyl alcohol 1 c c of 0 1 per cent sodium nitrite and 1 c c of the dimethyl alpha naphthyl amine reagent It is not necessary to treat the standard with trichloracetic acid copper sulfate or calcium hydroxide The trichloracetic acid in the milk filtrate is decomposed on hydrolysis and does not affect the final color The copper sulfate-calcium hydroxide treatment of the filtrate also does not influence the color production

RAPID BEDSIDE METHODS — Several rapid bedside methods of determination of the sulfonamide compounds have been introduced which except for slight variations or modifications are colorimetric methods based in principle upon the Marshall technique Schoeffel s micro technique consists of the use of a hanging drop and filter paper using micro amounts of the reagents listed under blood macromethod[34] Bul lowa and Ratish s test for sulfapyridine is based on the extraction of sulfapyridine from the blood with ether proceeding then with trichlor acetic acid sodium nitrite and urea and developing the final purple red color with dimethyl a naphthylamine The final color is compared with standards made up of aqueous phenol red[35] Hartman s method[36] utilizes a slightly different principle the addition of para dimethylamino benzaldehyde (Ehrlich s reagent) in acid solution to the blood or tissue fluid to produce a yellow color This test is based on the principle that the aldehyde group of the reagent reacts with the free amino group on the benzene ring of the sulfonamide compound The final color is read in a Klett Summerson colorimeter or against permanent standards made up of potassium dichromate This test is applicable qualitatively but quantitative estimations are not reliable For quantitative work Marshall s method is preferred After testing all the remedies included in New and Non-official Remedies Hartman found that urea acetanilid acetphenetidin and sodium nitrite may interfere with the test unless the fluids to be tested are diluted appropriately The most recent rapid bedside method by Sheftel[37] utilizes the same reagents as the Marshall test but in stable tablet form and a lucite wedge colorimeter for the final readings

By the above method of Marshall one cannot distinguish the identity of the various drugs Lott and Bergeim[19] however have given a test to distinguish between sulfapyridine and sulfathiazole The test consists of treating the sodium salts with cupric sulfate Sulfathiazole thereby forms a purple precipitate while sulfapyridine forms an apple green precipitate which gradually changes to greenish brown

FECES — Determination of the presence of these compounds in the feces may be performed by extracting them and warming with a 10 per cent solution of caustic soda diluting and determining as for blood[11] The method of Strauss and his associates[7] is to mix the total 24 hour quantity of feces with warm acetone dry to a constant weight and pulverize thoroughly Place 1 gram (duplicate) samples of the powdered feces in suitable containers preferably soxhlet thimbles and extract thoroughly with acetone Usually about 250 ml acetone and 16 hours or more of extraction are required to complete this process The acetone extract is diluted 1 10 with distilled water make determinations on 0 5 ml to 1 0 ml amounts Treat in the same manner as for blood filtrates

TISSUE ASSAY — When tissues are to be analyzed they should be weighed accurately on removal Tissue should be minced finely and ground with sand The ground tissue may be extracted three times with boiling distilled water or preferably in a soxhlet apparatus with a limited amount of alcohol In the latter method dilute an aliquot portion of the extract with water Both of the aqueous extracts may be treated exactly as for blood using a photoelectric colorimeter

BODY FLUIDS — The determination of the sulfonamide content of body fluids may be carried out in the same manner after deproteinization as for blood

BREAST MILK — To determine the sulfanilamide content of breast milk requires a special procedure because the original method of Marshall in which alcohol is used as a protein precipitant cannot be applied to milk because of its high fat content If trichloracetic acid is used as a protein precipitant the method works satisfactorily Pinto[13] has described a method for the determination of sulfanilamide in human skimmed milk which is quite accurate

Ten c c of protein free filtrate prepared by adding one volume of 20 per cent trichloracetic acid to one volume of milk and filtering is pipetted into a 25 c c volumetric flask Add 4 c c of 20 per cent copper sulfate and 4 c c of 20 per cent calcium hydroxide suspension If the calcium hydroxide suspension has not been prepared freshly more than 4 c c may be necessary to make the contents of the flask alkaline Shake frequently for one half hour dilute to 25 c c and filter Five c c of the

passage of the drug through the pylorus Dividing the dose of sulfaguanidine may increase its rate of absorption to give a higher blood level The sodium salts of sulfapyridine and sulfathiazole both of which are absorbed quite readily from the intestinal tract may be administered by mouth Sodium sulfathiazole by mouth may be absorbed so readily that *the subsequent blood curve of concentration* approximates that after intravenous administration of the salt

By the intravenous and subcutaneous routes all of these drugs except sulfaguanidine in the methods that have been used give prompt and high concentrations in the blood Sulfanilamide sulfapyridine sulfadiazine and sulfaguanidine enter more into the red blood cells than does sulfathiazole which is contained chiefly in the plasma of the blood a feature given as one explanation for the difficulty of maintaining a blood level with the latter drug As a matter of fact sulfadiazine by any mode of administration maintains its level in the blood better than any of the other drugs Glucose sulfapyridine does not diffuse as well as *sulfapyridine itself and* is found only in extracellular fluids *and not in* the red blood cells

By Intramuscular Dosage — The rate of absorption of the preparations used for intramuscular injections is quite rapid Thus neoprontosil the red sulfanilamide solution is absorbed in three to five hours Sodium sulfapyridine may be used for intramuscular injection as a 10 to 33 per cent suspension and is absorbed in 4 to 8 hours

By Rectum — Various studies have shown that sulfanilamide is the only one absorbed by rectum to an extent sufficient to warrant this route of administration clinically Sulfapyridine sodium sulfapyridine sulfathiazole sodium sulfathiazole sulfamethylthiazole and sulfadiazine are absorbed poorly and erratically from the rectum or sigmoid colon although several have advocated their use by this route

In careful studies of the administration of sulfanilamide by rectum *Turell Marino and Nerb*[40] *found the drug to be* absorbed readily from the rectum in an isolated rectal pouch and even with the presence of polyps They found a 1 per cent solution to be absorbed better from the colon than from the rectum In suppository form however little is absorbed from the rectum Proctoscopic studies following these procedures showed no significant changes in the normal mucosa of the lower intestinal tract

By Local Application — In the local application of these drugs there is slight absorption in the immediate vicinity of application but rarely sufficient to obtain any therapeutic blood level However if the drug is applied externally and given by mouth as well careful vigilance against

Pharmacology of Sulfonamides

The sulfonamide compounds though undergoing changes in the host cause no pharmacological actions of therapeutic benefit in therapeutic doses cause no discernible effects on tissues or organs but they do produce some chemical alterations in the body Their major action is upon bacteria

Their pharmacological activity depends to a great extent upon one variable factor, namely solubility, variable in the sense that each drug differs somewhat from the others in its solubility and chemical characteristics Because sulfanilamide was the first drug to be investigated actively and because of its most thorough study it is used as the parent substance for comparison of the other compounds In this discussion of pharmacology the 5 drugs sulfanilamide sulfapyridine sulfathiazole sulfadiazine and sulfaguanidine will be considered together, comparing the drugs in the various phases of their action

Absorption — In the human subject by any mode of administration sulfanilamide is absorbed readily and is diffused quickly through the body tissues

By Mouth — In this respect the drug has been compared to urea and to alcohol Using sulfanilamide as a standard the absorption of the related compounds when administered by mouth varies considerably There is little absorption of any of these drugs from the stomach wall although a blood level of 2 to 7 mgm per cent has been observed after oral administration of sulfapyridine in two cases with complete pyloric obstruction[33] When sulfanilamide is given as a single dose by mouth absorption from the intestine is fairly complete with the peak of blood level at the end of four hours Sulfathiazole does approximately the same a little more rapidly if anything but sulfapyridine is much more erratic frequently taking 6 hours for complete absorption Sulfadiazine is absorbed much the same as sulfanilamide from the intestine but sulfaguanidine is absorbed very poorly most of it passing out with the feces Once sulfanilamide is present in solution in the small intestine even in the presence of diarrhea or shock it is absorbed adequately[33] The simultaneous administration of oil with sulfanilamide or of alkali in the form of sodium bicarbonate or magnesium oxide but not enough to cause diarrhea with sulfathiazole has been found to hasten their absorption from the gastrointestinal tract of man The absorption of sulfapyridine by mouth can be improved oftentimes by grinding up the tablets and suspending the powder in water, milk or other fluid to facilitate

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output of ammonia interference with the tubular reabsorption of bicarbonate and bases with an increase in the alkalinity of the urine and a drop in the CO_2 combining power of the blood plasma. This is interpreted to mean that the drug causes acidosis and it has been advised to administer sodium bicarbonate to prevent or combat it. That alkali may not do so is shown by the studies of Bauer and Coggeshall[43] in which there still was an average reduction of CO_2 of 10 volumes per cent even though the patients received amounts of sodium bicarbonate equal to the sulfanilamide dosage. In subsequent studies Hartmann, Perley and Barnett[44] and Hartmann[45] have pointed out that patients taking sulfanilamide develop a hyperventilation. With hyperventilation the plasma CO_2 is blown off, the CO_2 combining power of the plasma falls, the pH of the blood rises and the urine becomes alkaline. Thus according to these authors the change in the acid base balance is considered to be one of a CO_2 deficit type of alkalosis rather than an alkali deficit type of acidosis. In a later study Beckman and Bauer[46] concluded that sulfanilamide does produce a primary alkali deficit type of acidosis. Thus the problem of sulfanilamide acidosis as yet is unsettled. Sulfapyridine, sulfathiazole, sulfadiazine and sulfaguanidine do not seem to cause any significant fall in the CO_2 combining power of the blood.

A metabolic action, an *antipyretic effect*, has been found with sulfanilamide, sulfapyridine and sulfathiazole. Sulfapyridine, which has the most antipyretic effect, was studied carefully by Beeson and Janeway[47]. In experiments with rabbits these authors found a dilatation of peripheral vessels leading to heat loss. Sodium sulfapyridine given intravenously at the height of fever induced by typhoid vaccine produced a rapid fall in temperature to normal and even to subnormal, but sodium sulfathiazole had only a slight antipyretic action under these circumstances. The acetyl salts of sulfanilamide, sulfapyridine and sulfathiazole had no effect by mouth, but the latter two were effective in lowering temperature when given intravenously.

Other metabolic effects on the blood and tissues have been studied. Sulfanilamide per se does not disturb the *cross matching of blood*. In a study of this in 24 cases Kreimin, Hamblen and Porcelli[48] concluded that it seemed that the inability to cross-match blood following the administration of sulfanilamide is due to changes in the blood brought about by the disease for which the drug was given rather than to the sulfanilamide itself. In customary therapeutic doses sulfanilamide causes an *acceleration of hemoglobin metabolism* characterized by an increase in urobilinogen in the feces and a varying increase in reticulocyte percentage. Certain *oxidation products* are found following the administration of the

toxic blood levels must be maintained These various modes of administration and the quantities to be used are discussed more fully under methods of administration and dosage for each drug

Effects after Absorption — After absorption has taken place by whatever route the drug was administered it remains *in the blood stream* for a variable length of time a feature highly important in their efficacy against bacterial infections The drug is contained in both the red cells and the plasma varying somewhat in relation to the water content of those elements When blood containing these drugs is allowed to clot the compound is distributed almost evenly between clot and serum However none of these drugs penetrate formed blood clot appreciably[41] The blood level of drug effective against infection depends upon the rate of absorption degree of acetylation and the speed of elimination by the kidneys Considering these three factors sulfanilamide gives the most uniform concentration With sulfapyridine the blood level cannot be predicted because of variations in all these factors With sulfathiazole the blood level is difficult to maintain because of its rapid excretion by the kidneys With sulfadiazine on the other hand due to decreased renal excretion the blood level is maintained with ease In fact care must be taken to prevent unnecessarily high levels Adequate blood levels are difficult to obtain with sulfaguanidine unless the drug is given in small divided doses

In the blood certain changes may take place with the various compounds That sulfanilamide and related substances undergo and induce chemical changes in the body is indicated clearly by acetylation esterification by effects on metabolism such as the influence of sulfapyridine on fever or as is reflected in the excretion of porphyrin Further changes are evident by some as yet unexplained reaction involving oxidation reduction processes the most striking of which is methemoglobin formation Sulfonamides in large doses lower the oxygen saturation of the blood and administration of oxygen will raise the saturation of that portion of the hemoglobin not already influenced by the drugs

Sulfanilamide is the only one of the 5 drugs that has been found under certain circumstances to *lower appreciably the CO combining power* of the blood plasma Whether this demands the administration of alkalies has been a point of considerable controversy Early in the studies of sulfanilamide toxicity it was demonstrated by Southworth[42] that a lowering of the CO_2 combining power of the blood plasma occurs frequently with most of the toxic manifestations Long and Marshall and their associates have found that following sulfanilamide administration there occurs an increase in the excretion of sodium a reduction in the

concentrated in the bile and gall bladder. In therapeutic doses they have not been found to affect liver function. With the idea that the failure to obtain satisfactory absorption and resulting blood concentration from sulfaguanidine may be due to removal of the drug from the blood stream by the liver and its return to the intestinal tract in the bile flowing through the biliary ducts, Hubbard, Butsch and Aaron[31] studied two patients with T tubes in place in the common duct. They found their hypothesis to be incorrect, for there was very little sulfaguanidine contained in the bile.

Sulfapyridine, sulfathiazole and sulfadiazine have been found to occur in adequate concentrations in the pleural, peritoneal and pericardial fluids. In a study of patients with sulfathiazole conjunctivitis, Turkell and Wilhelm found sulfathiazole secreted in the tears in concentrations of 0.1–0.98 mgm per cent, but not a cause of the conjunctivitis. Insufficient studies have been carried out up to the present time to determine the concentrations of these drugs in ratios compared to sulfanilamide in the many other body fluids and secretions.

The amounts secreted by the kidneys into the urine will be discussed further on under excretion of these drugs. Suffice it to say that usually some amount of these drugs is contained in all of the body fluids, whether the fluid is physiological or pathological. The conjugated acetyl products of these drugs generally diffuse less readily into the body fluids than do the free forms.

Sulfanilamide, the parent substance, has been found to be *excreted in the breast milk* of lactating women, and here it has occasioned considerable interest because of the possibility of therapeutic effect and toxicity upon the nursing infant. The level of sulfanilamide in breast milk has been found to be considerably higher than that in the blood. After a constant blood level has become established, the drug is excreted in the milk at a definite concentration per cubic centimeter rather than per total volume. The acetyl form in the milk may vary from 35 to 83 per cent, and it tends to reach its highest level in the fourth or fifth day after the beginning of administration. The excretion of sulfanilamide in breast milk may continue for 48 hours after the drug has been stopped. Concerning the therapeutic possibility, Foster[33] believes that not much more than one gram daily would be ingested by the child. Since the usual therapeutic dose for an infant is from 7 to 15 grains (0.5 to 1.0 gm.) daily, perhaps little can be expected in a therapeutic way from administration of this drug to the child by suckling. Hac and her associates found the amount in milk so small, never greater than 1.6 per cent of the total dose ingested by the mother, that they concluded that

sulfonamide drugs Many urines from patients receiving these drugs particularly sulfanilamide darken on exposure to air examination of the inorganic and ethereal sulfates shows a much lower ratio than the normal 10 1 From urines of this type *acetylhydroxylamino benzene sulforamide (1 4)* and *para aminophenol* have been isolated the latter particularly from cyanosed patients A *purplish pigment* of the indophenol class may occur also but its exact composition is not yet known[41] These various chemical and metabolic alterations following administration of these drugs are related to the blood concentrations of the sulfonamide substances

In the transportation of the sulfonamide compounds in the blood stream through the body their concentration and *effects on organs tissues* and *body fluids* have received considerable attention Again using sulfanilamide as the basis for comparison this drug has been found to become distributed widely throughout the body It may be stated that sulfanilamide and its conjugated derivative the acetyl salt have been identified in practically all normal and pathological fluids It has been found that saliva pancreatic juice bile pleural fluid edema fluid prostatic and cervical secretions and cerebrospinal fluid contain the drug in a concentration that is nearly the same as or only slightly lower than that of the blood Skeletal muscle heart muscle liver lung and spleen contain a concentration approximately equivalent to that of the blood In the skin and brain on the other hand the concentration is much less than that in the blood, while bone and fat contain only small amounts Sulfapyridine attains much the same concentrations except for its higher content in the liver and kidney substances Sulfathiazole also is present in the kidney in two or more times the blood concentration and in addition diffuses with difficulty into the cerebrospinal fluid This observation as pointed out by Sadusk Blake and Seymour[40] has practical significance in that it suggests the possibility that it may not be a satisfactory agent for the treatment of meningitis In a few isolated instances however it has been found to be effective in meningococcal infections Although sulfathiazole does not seem to diffuse readily through normal meninges its ability to penetrate diseased meninges has not received as yet adequate study

Sulfaguanidine likewise penetrates slowly into the brain and spinal fluid With the exception of brain and spinal fluid the rapid penetration and nearly equal distribution of sulfaguanidine is similar to that found for sulfanilamide and sulfapyridine Sulfadiazine passes over into the spinal fluid in concentrations of from ½ to ⅔ of that which exists in the blood

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probably there is little danger to the nursing infant unless the child should be unusually susceptible to sulfanilamide There is little likelihood of any injury from the amounts of the drug obtained in the milk and it seems clear that the breast milk would not be a practical medium for the administration of sulfanilamide to the infant On the other hand Stewart and Pratt[5] found that breast fed babies of full time nursing mothers did show clinical evidence of toxic manifestations when sulfanilamide occasionally reached concentrations of 7 mgm per cent in the breast milk A single instance of toxicity (?) on small doses of sulfanilamide from a mother to an infant has been reported[56]

Numerous reports have indicated that sulfanilamide passes readily through the placenta and appears within five hours in nearly equal concentrations in the fetal and the maternal blood at term

These drugs with rare exceptions cause no action or histological lesions of any moment in the various *organs* of the body when present in therapeutic levels in the blood When tested on animals they have been found to have no significant effects on the heart respiration blood pressure smooth muscle uterus parenchymatous organs renal function hematopoietic system or central nervous system Any changes brought about occur either with large amounts of the drug or with a toxic reaction A toxic reaction may result from idiosyncrasy to the drug (hepatitis) or from mechanical effects (sulfapyridine sulfathiazole crystals in the kidneys) or may occur with therapeutic doses if the organ is diseased as in cardiac hepatic or renal insufficiency With either of these diseased conditions a therapeutic dose may result in abnormally high blood levels

Because of the nausea and vomiting encountered so frequently with sulfapyridine the *stomach and its functions* have been studied in various ways As with sulfanilamide in dogs in which Carryer and Ivy[57] found a high concentration in the gastric juice 6 hours after its oral administration similarly sulfapyridine may be found in the stomach secretion in twice the concentration in which it is present in the blood Thus the gastric mucosa is found to secrete these drugs under certain circumstances although no histological changes have been noted Sulfapyridine has been found also to delay the emptying time of the stomach When given in 1 gram doses in a motor meal of farina and barium sulfate to 10 healthy adults although the blood level averaged only 1 8 mgm per cent there was an average delay of 28 per cent in gastric emptying in every case when compared with the controls[58] This may be a factor in sulfapyridine vomiting although in dogs vomiting occurs with the drug even though the stomach has been resected and sulfapyridine is administered intravenously Direct application of this drug to the vom

iting center in the brain[49] does not cause vomiting so the cause of this disturbance after sulfapyridine has not yet been elucidated It is thought likely to be due to an extra gastric reflex

In numerous studies that have been carried out on *bone marrow* following sulfanilamide administration both stimulation and depression have been described in various animals In 9 human subjects all of whom however were ill Faul and Limarzi[50] observed that therapeutic dose of sulfanilamide produced a moderate normoblastic bone marrow hyperplasia with most of these cells at the orthochromatic stage with an increase in mean corpuscular volume of the blood and a slight increase in mean red cell diameter

Early in the studies of the sulfonamide compounds Viconi[61] stated that sulfanilamide affects *spermatogenesis* decreasing the number and viability of spermatozoa In more recent studies sulfanilamide[67] and sulfapyridine[63] have been found to have no deleterious effects on spermatogenesis and concentrations of these drugs as high as 160 mgm per cent had no effect in vitro on the survival or activity of human spermatozoa

The sulfonamide compounds are foreign to and chemical poisons to the human organism As such the body attempts to eliminate their toxic features by a process long known in pharmacology as *detoxification* In their circulation through the body by a process of reduction the corresponding acetyl salt of each compound is formed To this process of detoxification has been given the name *acetylation* At first it was speculated and later it was demonstrated by Stewart Rourke and Allen[64] that the liver probably is the site of this conjugation

In studying the similar changes occuring with sulfapyridine James[31] made the premise that this compound might be detoxicated by conversion to a methyl derivative as in the detoxication of quinoline and other substances By a lengthy process of urine extraction only sulfapyridine and acetylsulfapyridine could be recovered with the conclusion that it was not decomposed into sulfanilamide or other products of schism

The process of acetylation in the body evidently is reversible because after the administration of acetylsulfanilamide to animals sulfanilamide can be found in small amounts in the blood and the same is true for man[6] According to F Henderson about 40 per cent of N^1 acetylsulfanilamide is hydrolyzed in the human body to sulfanilamide and a part of this is converted to N^4 acetylsulfanilamide Although sulfanilamide has been used as the example drug all the other compounds under discussion undergo the same process in varying degree however

By whatever route these drugs are administered the mono-acetyl amino derivative appears in the urine of man rabbit mouse cat fish

chicken, rat pig goat cow horse and monkey The dog and the frog do not acetylate these compounds readily In the human patient the degree of acetylation of sulfanilamide is variable between 10 and 15 per cent in the blood 50 per cent in the urine The amount of acetylation does not depend upon the concentration in the blood stream The presence of increased serum bilirubin does not appear to change the rate of acetylation Acetylsulfanilamide has no therapeutic usefulness and ordinarily is non toxic unless an occasional individual should acetylate more than the average when toxic symptoms might result from this cause[66] In animals and in man acetylsulfanilamide is capable of lowering the CO combining power of the blood Acetylsulfanilamide is quite soluble in aqueous solutions

The acetylation of sulfapyridine on the other hand is very erratic ranging from 15 to 75 per cent of the drug As time goes on the conjugation and hence the amount of acetylsulfapyridine, increases Increasing acetylation may give a falling concentration of free sulfapyridine in the blood The importance of recognizing this fact in therapeutics is pointed out by Blake[67] in that if blood levels of the free drug are used as guides to the amount and spacing of dosage a low or falling concentration of free sulfapyridine may be regarded mistakenly as an indication for increasing the dosage when in fact, the total concentration of the drug is rising This can lead to toxic effects

Acetylsulfapyridine likewise is therapeutically inactive It has a low solubility in aqueous solution and hence produces toxic effects by forming concretions in the urinary tract In this connection it is of interest that when sodium sulfapyridine is administered the degree of acetylation in both the blood and urine is distinctly less than when sulfapyridine is used in the same manner The therapeutic implication is clear When carefully looked for the crystals of acetylsulfapyridine may be found in the urine of all persons taking this drug

With sulfathiazole the degree of acetylation in the blood and urine is somewhat comparable to that of sulfanilamide but definitely much less than that of sulfapyridine The degree of acetylation usually falls into the range of 0 to 30 per cent the median being approximately 12 per cent The relative amount of conjugated sulfathiazole and likewise of sulfamethylthiazole tends to remain small in the blood regardless of the route of administration unless kidney function is depressed In patients in whom the rate of excretion of the drug is decreased the conjugation of sulfathiazole tends to increase rapidly if the drug remains in the body for any considerable period of time Long[68] suggests that the reason why sulfathiazole does not seem to be converted ordinarily in large

amounts to the acetyl form is that the drug usually is excreted so rapidly that the conjugating mechanism in the liver does not have time to play its ordinary role. Acetylsulfathiazole is therapeutically inert also and it is approximately three times less soluble in water than acetylsulfanilamide. Its insolubility gives rise also to concretions in the urinary tract but perhaps somewhat less than sulfapyridine due to the lesser degree of acetyl salt formation.

Sulfadiazine is conjugated somewhat less than sulfanilamide and in the urine about 1/3 of the drug exists in the acetylated form. Only small amounts of acetylsulfadiazine are found in the blood because this compound is excreted quite easily when renal function is normal. Because acetylsulfadiazine is much more soluble in water than any of the other compounds, it should make kidney damage from concretions less probable.

At the time of this writing the acetylation of sulfaguanidine had not been studied extensively except to state that its conjugation is similar to that of sulfanilamide.

In summary it may be stated that there are wide differences in the *degree of conjugation* of these various drugs as found in the urine, particularly during the first 24 hours after their administration. The smallest percentage of conjugation in the urine of the human is to be found with sulfathiazole, the largest with sulfapyridine. Sulfamethylthiazole is apt to show slightly more conjugation than sulfathiazole and sulfanilamide somewhat less than sulfapyridine. In the case of each drug the *percentage of the excreted drug which is conjugated is essentially the same regardless of the route of administration*[27].

The *excretion* of these drugs from the body is chiefly by way of the kidneys. The exception to this is sulfaguanidine, the greater part of which remains in the intestinal tract and is excreted with the feces. That which enters the blood stream, however, also leaves by way of the urinary tract. With all of the sulfonamide compounds the time of maximum urinary excretion varies with the drug given, the dosage and the route of administration. It varies also in individual subjects, but the maximum excretion occurs always within the first 24 hours.

The per diem fluid intake has more effect on the sulfanilamide excretion in the urine than it does on the blood level. Both blood and urine levels are influenced but the urine more, inasmuch as forcing of fluids within limits increases the excretion and curtailing of fluids decreases the excretion of sulfanilamide by the urine. Forcing fluid beyond given levels acts as a diluent. This will be discussed further when treatment of urinary tract infections is described.

In terms of *renal function clearance* of the sulfonamides has been studied in comparison to creatinine clearance. The clearance of sulfanilamide is 20 to 30 per cent of creatinine clearance. In similar comparative studies sulfapyridine clearance has been found to be 16 to 39 per cent. These data indicate that the drug is excreted entirely by glomerular filtration and that 70 to 80 per cent in the case of sulfanilamide and 60 to 85 per cent in the case of sulfapyridine is reabsorbed by the kidney tubules. In the case of glucose sulfapyridine the drug is excreted very rapidly with practically no reabsorption in the kidney tubules. The data for sulfathiazole indicates that in general there is less tubular reabsorption of this drug than of either sulfanilamide or sulfapyridine. Its rate of excretion seems to lie between those two drugs. With sulfadiazine the excretion by the kidney is relatively slow. Because of the difficult attainment of blood levels with sulfaguanidine adequate renal excretion studies have not been carried out. In one experiment it is interesting to note however that over 95 per cent of the amount of sulfaguanidine given intravenously was excreted in the urine in 24 hours.

The acetyl salts of some of these compounds have a greater rate of renal clearance than the free form indicating less tubular reabsorption.

With renal function impaired there is a diminished excretion of the drugs and a consequent retention with resulting elevation of blood concentration in the body. When this occurs there develops an increased rate of conjugation with a rise in the amount of the acetyl salt circulating in the blood stream. With the rate of excretion so variable from drug to drug and from individual to individual Alyea and his associates studied and found a comparison between sulfanilamide excretion and phenolsulphonphthalein excretion[60]. In impaired renal function Alyea standardizes the sulfonamide dosage on the basis of the phthalein excretion curve. He considers 50 to 60 per cent excretion of phenolsulphonphthalein in the first half hour as normal. The first day's dose of sulfanilamide is selected arbitrarily on the basis of 15 grains (1.0 gm.) for each 10 per cent phthalein excretion in the first one half hour and the subsequent daily dosage is established as half this amount. Thus a patient with a 60 per cent phthalein excretion would receive 90 grains (6.0 gm.) the first day and 45 gr. (3.0 gm.) daily thereafter. When renal function is impaired for example to 40 per cent in the first half hour Alyea uses 60 gr. (4.0 gm.) the first day and 30 gr. (2.0 gm.) daily and so on. With this method he claims to achieve remarkably constant blood levels. Although applied originally to sulfanilamide it is applicable to sulfapyridine and probably to sulfathiazole also.

In one of the very first reports on prontosil in the German literature

an acute nephritis was reported as the result of the drug therapy. This was in a case of scarlet fever, however, and the nephritis may have been due to the scarlet fever. *Renal complications* from sulfanilamide have not arisen, but the conjugated salts of sulfapyridine and sulfathiazole have given rise in a small percentage of cases to hematuria, renal colic, anuria, azotemia and even death. These complications are the result of crystallization of acetylsulfapyridine or acetylsulfathiazole in the kidney and urinary tract. There is a distinct relationship between the amount of the drugs given, the rate at which acetylation proceeds and the amount of crystals deposited in the urine.

The crystals of acetylsulfapyridine usually are colorless and appear as flat, thin plates with a sharply elliptic outline. They are precipitated from both acid and alkaline urines, and changes in reaction do not alter their physical characteristics. Upon fractional analysis of urine containing crystals it has been demonstrated that the crystals consist almost entirely of acetylsulfapyridine.[2] These calculi cannot be detected in the urinary tract by routine kidney, ureter or bladder x-rays. Pathologically such crystals cause certain changes in the kidneys, chiefly by a mechanical effect but also by chemical action. There develops a striking dilatation of the glomerular spaces and tubules, a thickening of the basement membranes of the glomerular tufts and changes in the shape of the cells of the capsular epithelium. The material probably is precipitated in the proximal portions of the tubules, collects in the loops of Henle and the smaller collecting tubules and causes plugging of these excretory ducts. The result of this is marked dilatation of the tubules and glomerular spaces. The greatest danger, however, appears to occur in the renal pelves and ureters, for here concretions form with denuding of epithelium, mucosal hemorrhages, the presence of clotted blood and marked edema. In the majority of histological reports crystals ordinarily were not seen in the kidney substance. This has been due apparently to the technique used in preparation of the tissues. For when Stryker[71] employed a rapid celloidin technique to avoid long exposure of tissue to water or to solutions which dissolve the material, he was able to demonstrate the acetylsulfapyridine crystals in the kidney substance. It has been demonstrated that sodium sulfapyridine is apt to cause more acetyl crystals than does sulfapyridine and, when used in comparable doses, is more likely to produce toxic urinary symptoms than does sulfapyridine.

Sulfathiazole, though not quite as apt as sulfapyridine to cause the renal complications, does give rise to much the same sequence of events. The uroliths of sulfathiazole have been found in their composition to contain 4.2 per cent free and 25 per cent conjugated drug and some

water insoluble material in part lipoid The changes in the kidney caused by acetyl sulfathiazole are similar to the changes from acetyl sulfapyridine except that with the former recrystallization is chiefly in the kidney tubules whereas in the latter it is most frequent in the renal pelves and ureter[7]

To this process of crystallization of these two drugs with the resultant toxic manifestations Gross Cooper and Scott[73] have given the name 'urolithiasis medicamentosa This will be discussed further under the discussion of toxic manifestations of these drugs

It has been observed that shortly after the administration of sulfanilamide it appears *in the skin* It is excreted readily in the *sweat* in concentration of one half to two thirds of the blood level[74] By a sweating procedure sulfanilamide can be made to reappear in the blood urine and sweat days after it has been stopped and the blood level has been zero

Some *excretion in the feces* takes place with all of these drugs Sulfaguanidine is found in the highest concentration in the stools sulfapyridine to about 35 to 40 per cent sulfathiazole in large amounts if the blood level is low and sulfanilamide in traces Sulfadiazine is excreted in the feces in much the same way as sulfanilamide

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Mode of Action of Sulfonamides

By what action the effect of sulfanilamide and its related compounds is accomplished in the animal organism or human patient as yet has not been established definitely In this connection it may be fair to state that for perhaps no drug that acts with any degree of specificity do we know the actual ultimate cellular response Nevertheless the question of the mode of action of the sulfonamide compounds has been a stimulating challenge to scientific medicine which has resulted in much interest and numerous hypotheses These various hypotheses[551] all containing far reaching truths have approached the problems from different viewpoints yet none of them answers all the questions concerning the data of the many scientific facts that have been accumulated It should be borne in mind that the discovery and certain findings concerning the therapeutic action of sulfanilamide were made in the laboratory by experiments on animals and in the test tube and that much of the detailed information so acquired cannot be applied as yet to human subjects

In discussing the mode of action of these drugs it may be well to record first certain phenomena that have been observed and experiments that have been carried out in this direction and then to set down the various theories that have been postulated to explain these phenomena

Domagk s original communication stated that *phagocytosis* by leukocytes played an important role in clearing the tissues of streptococci in mice treated with prontosil Quite promptly it was shown that phagocytosis does not explain adequately the entire phenomenon because normal serum from which the leukocytes have been removed is just as effective a vehicle as whole blood for the action of sulfanilamide on streptococci On the other hand if a mouse is deprived of its polymorphonuclear leukocytes as accomplished by the administration of benzene adequate therapy with sulfanilamide is unavailing the streptococci continue to multiply slowly and the mouse dies in from three to four days This indicates that *bacteriostasis* alone is insufficient and that the presence of the leukocytes is necessary if the infection is to be brought under control The experimental work in the test tube and the laboratory animals proceeded hand in hand One of the original observations was that in mice when sulfanilamide is given immediately after experimental infection it has a protective action as long as the chemical is given in that the animals survive after as much as several thousand minimal lethal doses of streptococci Unit for unit this was a much more powerful effect in the animal body than could be demonstrated in

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the test tube in fact an in vivo enhancement or increased potentiation of the action of the drug For the concentration of drug necessary to produce a bacteriostatic or bactericidal action in vitro may have absolutely no apparent relation to that necessary for its activity in vivo Neither has a relationship been demonstrated between chemical structure and specific activity Furthermore compounds may be very active in vitro and inactive in vivo On the other hand if the administration of th drug was delayed for several hours or the treatment was stopped prematurely invariably the mice died The first part of this latter finding, namely delayed administration allowed death to occur was to be explained by the test tube finding that these drugs using sulfanilamide as the example possessed a latent phase in their action That is to say when drug and susceptible organisms are cultured together the organisms continue to grow at their normal rate for a period of several hours an apparent lag in the action of the chemical On the other hand an inoculum composed of bacteria obtained from sulfanilamide containing media during bacteriostasis on subculture in fresh sulfanilamide containing media responds at once to the drug without the usual lag phase of growth Following this lag phase growth and multiplication of organisms was found to be distinctly inhibited depending upon the size of the culture and the concentration of the drug present If a large inoculum of bacteria was used the drug was found to have no effect Then it was learned that the culture medium made a tremendous difference in the efficacy of the drug s action

The persistence of organisms in the test tube or in the animal body produced the evidence that these drugs had slight bactericidal or organism killing effect but that their action was chiefly bacteriostatic or organism inhibiting the addition of the highest possible concentration of dissolved sulfanilamide to a fully grown culture of bacteria does not bring about destruction of the organisms and does not alter appreciably their virulence This is one of the basic differences between the action of the sulfonamide compounds and that of most antiseptics With some organisms the bacteriostatic effect may result in morphological capsular and growth changes For example streptococci may show increased length of chains swelling and staining alterations Meningococci may swell may become irregular or pyriform in shape and manifest staining abnormalities Evidently microorganisms showing these degenerative changes lose little or none of their virulence when transferred to a sulfonamide free environment If the organism was not being eradicated from the body and yet the animal (patient) was recovering it was reasoned that body immunity must play a rôle A study of body immunity

revealed that these drugs e g sulfanilamide had no effect on the production of antistreptolysin that there was no stimulation or depression of the reticulo endothelial system and that body immunity was not influenced It was found that body immunity in the infections studied progressed at much the same rate of speed as had been found with these infections before the advent of the sulfonamides into medicine However it became appreciated that the drugs kept the organisms in check perhaps by partial destruction but chiefly by inhibition of proliferation until immunity had developed to overcome the infection this is the explanation to the second part of the premise above namely that if drug therapy was stopped prematurely the animals died These drugs do not inhibit to any extent or neutralize toxins or hemolysins produced by organisms A decrease in toxin or hemolysin production appears to be due to a decrease in the growth rate of the organism

Within certain limits that is type of organism and size of the inoculum the more virulent the organism to human tissues the more effective is sulfanilamide in causing bacteriostasis Its effect in the tissues depends upon the concentration in the blood stream and tissue fluids and the type of lesion in the tissues In previous summaries of this subject the writer has stated that the effective action of the sulfonamide compounds is mediated chiefly through the blood stream This statement has been challenged by others particularly with reference to urinary tract infections on the premise that concentration of the drug in the urine was an essential requirement of its action in that system That infection can be present in the urinary tract and that such an infection can be cured without any urine containing sulfanilamide passing through that tract has been demonstrated amply by the case report of Nesbit[7] A white male of 48 who had had a bilateral ureterosigmoidostomy for two years because of an intractable cystitis developed acute gonorrhea with prostatitis and epididymitis Twenty three grams of sulfapyridine over 8 days gave a complete clinical cure without recurrence forcing one to the conclusion that the site of action of the drug was in the tissues since the urine was evacuated by way of the bowel Further evidence that definite levels of concentration of the drug in the urine are not essential for the cure of urinary tract infections has been presented by Alyea and Roberts[7] and Helmholtz[8] Alyea and Roberts reduced the oral dose of sulfanilamide to the point where urine levels of the drug were as low as 30 mgm per cent and claimed results just as good as with the usually proposed higher levels In cases with kidney damage where high concentrations in the urine cannot be attained or may be harmful Helmholtz found very small doses with urine levels of 10 mgm

per 100 c c of urine well within the range of therapeutic usefulness in urinary tract infections Hence the importance of blood and tissue fluid concentrations

In the presence of elevated temperatures and high concentrations the drug may be somewhat bactericidal also White and Parker[79] found that in a broth culture at 40° C with a blood concentration of 10 to 20 mgm per cent of sulfanilamide a definite bactericidal effect can be obtained while only a bacteriostatic effect is evident under the same conditions at 37° C This is in vitro In vivo in rabbits the blood sulfanilamide level is unaffected by coincidental fever therapy except for a slight lowering due to slowed absorption of the drug from the gastrointestinal tract Fever in the human patient however has not seemed to increase the bactericidal effects of a given blood level

The type of tissue lesion is of vast importance in determining the effectiveness of these drugs as pointed out by Lockwood[80] In diffuse infections such as cellulitis lymphangitis erysipelas lobar pneumonia acute pyelonephritis or infections of the cerebrospinal fluid which are characterized by rapid multiplication and dissemination of invasive bacteria in tissues of relatively normal architecture and where there is no extensive tissue destruction or in fluids closely resembling normal serum or lymph the disease is likely to respond favorably to sulfonamide chemotherapy He states further that whether the causative organism is a hemolytic streptococcus staphylococcus or pneumococcus perhaps makes some difference in the choice of the drug but these lesions generally are susceptible regardless of the bacterial species To state this feature of action in another way there are at least three factors involved in the pathogenic activity of the more virulent streptococci 1) the production of a hemolytic toxin capable of causing the destruction of red blood cells 2) an erythrogenic factor responsible for skin rashes as scarlet fever etc 3) the property of invading tissues termed invasiveness which if maintained leads to tissue destruction pus formation or in the severe t instances to septicemia when the blood is invaded Sulfonamide chemotherapy is of the greatest value in combating the invasive factor unless there is much tissue destruction and the destroyed tissue is removed and of much less value when the other two predominate[81]

Thus far all investigators have agreed that bacteriostasis was the effective method by which these drugs act Originally it was suggested that these compounds changed or destroyed the capsules of virulent microorganisms but that idea soon was dispelled How bacteriostasis was brought about could not be answered It was argued also that the compounds exert this antibacterial effect by interfering with the normal

metabolism of the bacterial cell Whether this was due to the direct action of the sulfonamide on the bacterial cell or due to an intermediate product has led to the theories of Lockwood[75] Locke Main and Mellon[5] Woods[83] Fox[84] and others

For easy reference these hypotheses may be referred to as the peptone theory the peroxide catalase theory the para aminobenzoic acid theory the antianhydrase theory and the oxidation theory All of them are supported by sound reasoning and experimental data several of them are interrelated in certain thoughts and ideas but no one of them up to the present time explains all the facts Perhaps no one theory ever will cover all the facts of the subject but with the eagerness with which studies are being carried out in this regard it is to be expected that our knowledge of the mode of action of these drugs and later other drugs will advance rapidly Again it will be gained in all probability through chemistry

Peptone Theory — In 1938 Lockwood and his associates at the University of Pennsylvania initiated the thought of some substance interfering with or inhibiting sulfanilamide action They noted first that normal human serum with and without sulfanilamide was not a favorable culture medium for strains of hemolytic streptococci This was in confirmation of Bainbridge s earlier work[85] that some species of bacteria are unable to break down protein molecules to obtain essential nitrogen and literally starve to death unless predigested protein such as peptone is supplied to them Lockwood noted that the presence of small amounts of peptone prepared by enzymatic digestion of casein or lean meat would diminish significantly the bacteriostatic effect of sulfanilamide on hemolytic streptococci in human serum and peptone of this type has been used commonly in bacteriological culture media as a means of supplying readily available nitrogen to types of bacteria which like hemolytic streptococci are not equipped with active proteolytic enzymes with which to convert complex protein into utilizable amino acids The fact that effective sulfanilamide action depends upon the exclusion of added peptone suggested to these authors that the drug must act in some way through interference with the ability of the bacteria to utilize the traces of assimilable nitrogen which they found to occur in whole blood serum urine and other body fluids As explanation for this they assumed that sulfanilamide combines in some way with the free amino-nitrogen of protein degradation products and thus renders them unsuitable for bacterial utilization To put it another way sulfanilamide acts by interfering with the nutritional requirements of susceptible bacteria The addition of peptone to the medium supplies such an excess of assimilable nitrog

enous material that the bacteriostatic effect of the drug is largely nullified Later Lockwood used the term peptone as meaning any product of protein digestion and he found that the principle of peptone antagonism of sulfonamide bacteriostasis applied to sulfapyridine and sulfathiazole as well as to sulfanilamide and to pneumococci staphylococci and colon bacilli as well as to hemolytic streptococci He accepted it therefore as a general phenomenon[86]

This observation is highly significant in that it has focused interest on the practical fact that the sulfonamide compounds are only slightly effective against bacteria in areas with tissue necrosis and purulent exudate Hence for better and effective action of these drugs local collections of pus and exudate should be removed

Interesting as this observation is full confirmation has not been obtained for Fuller Colebrook and Maxted[87] were unable to substantiate it in fact they were able to kill bacteria with sulfanilamide in certain media that contained large amounts of peptone and protein breakdown products Bullowa and his associates[88] and Spring Lowell and Finland[89] failed to observe sulfapyridine inhibition with added peptone The same has been observed for sulfathiazole in the urine[90] The fact that the inhibition of sulfanilamide is not dependent on the presence of easily assimilable nitrogen has been shown by MacLeod[91]

In an attempt to be a little more specific than peptone Bliss and Long[92] studied the growth of organisms in media containing singly and in combination the ten essential amino acids Of these they found methionine to be the most effective in preventing sulfanilamide action How it was brought about was not known

The theory that sulfanilamide acts by interfering with the proteolytic enzyme of the coccus does not explain all the facts yet credit is due to Lockwood and his associates for stimulating a search for substances that inhibit the sulfonamide compounds This will be discussed further under para aminobenzoic acid

Peroxide catalase Theory — In the same year 1938 the peroxide catalase theory of sulfanilamide was proposed by Mellon and his associates[93] at the Mellon Institute in Pittsburgh Beginning with the oxidation reduction potentialities of sulfanilamide the various phenomena of sulfonamide action are explained as follows The NH_2 otherwise known as the free amino group is susceptible to varying degrees of oxidation The first step in its oxidation is the formation of NHOH an intermediate product called hydroxylamine derivative This derivative they have found to be enzyme poisoning in its effects being particularly active against the enzyme catalase Under clinical conditions virtually all th

bacteria that are affected permanently by sulfanilamide are aerobes rather than anaerobes. Now the normal function of the enzyme catalase is to destroy hydrogen peroxide that is liberated by the bacterium. The failure of catalase to neutralize peroxide results in an accumulation of the peroxide and it is to this factor that the bacteriostatic effect of sulfanilamide is attributed. The hypothesis promoted by these observers is that the sulfanilamide is altered by the oxidative processes in the cells to become anti catalase. Hence the introduction of sulfanilamide becoming an anti catalase acts on catalase to prevent the neutralization of peroxide which deranges the normal process in such a manner that the organism becomes surrounded by a high accumulation of hydrogen peroxide. The effect of such an accumulation is to render the organism more vulnerable to the anti bacterial defense mechanism of the host which eventually completes its destruction. These authors have found accumulations of peroxide in cultures of pneumococci and streptococci effected by sulfanilamide.

In this enzymatic concept of the mode of action of sulfanilamide a time factor was postulated for the conversion of the inactive sulfanilamide to an active anti catalase which was presumed to result through the oxidation to the hydroxylamine derivative. This furnished an explanation of the characteristic lag period preliminary to the bacteriostatic action of the drug. This was borne out by the finding that the sulfonhydroxamides in the absence of blood were bacteriostatically effective without a lag period. In a study of such compounds these authors found a hypothetical compound to eliminate the lag period in p caproylamino benzenesulfonhydroxamide. This substance was pre formed in the sense that it possessed the group or groups necessary to bacteriostatic activity which are normally formed by the microorganism itself but was impractical because of its instability and transient effect[93]

According to this theory one would expect that organisms that are active producers of hydrogen peroxide would be susceptible to sulfanilamide whereas poor producers would be resistant. This idea is supported by the work of MacLeod[34] who reported that a sulfapyridine susceptible strain of type I pneumococcus produced large quantities of hydrogen peroxide whereas a resistant strain of identical virulence produced little or none. One of the essential conditions for the formation of hydrogen peroxide is the presence of oxygen which fact would explain the lessened activity of sulfanilamide under conditions of diminished oxygen tension.

Since the hydroxylamine derivative is an intermediate product of sulfanilamide oxidation further oxidation converts it to the nitroso derivative. This compound is capable of oxidizing hemoglobin to methemo

globin and according to the authors, appears to be related closely to the oxidation products responsible for the cyanosis after sulfanilamide To this nitroso compound they attribute most of the toxic symptoms

In studying sulfapyridine and other related compounds in this connection Mellon found that all of those substances which have a free amino group in the position para to the sulfonamido group had anticatalase activity and attributed the bacteriostatic effect to this property

It is to be noted that this theory like Lockwood s, introduces a third substance between sulfanilamide and bacterium in this instance hydrogen peroxide and further is based on the assumption that oxygen is most essential a feature that will be discussed under Fox s hypothesis oxidation theory That Mellon s theory likewise does not explain all the facts may be seen from the fact that type III group A hemolytic streptococci as a class fail to produce detectable amounts of peroxide and yet they are very sensitive to the bacteriostatic activity of sulfanilamide

Para aminobenzoic Acid Theory — In 1939 Stamp[9] in the laboratories of the University of London seeking an inhibiting substance undertook to isolate from bacterial cells a substance responsible for their antibacteriostatic activity He discovered that the extraction of hemolytic streptococci in bulk with dilute alkali yielded a precipitate which contained an extremely active inhibitor of sulfonamide effects Under his experimental conditions a concentration of 1 0 milligram per 100 c c of this extract was approximately equivalent in anti sulfonamide effect to 100 milligrams of peptone In a preliminary chemical analysis it was concluded that the material was heat stable and free from protein consisting of a mixture of substances of relatively low molecular weight including free amino acids' Stamp believed that this extract contained either a necessary nutritive factor a rarer amino acid which the bacteria could not synthesize or a co enzyme upon which the activity of an essential enzyme might depend

Extracts with similar non specific properties have been obtained from *Brucella abortus* by Green[96] On direct extraction of bacteria it was found that when *Br abortus* was allowed to autolyze in water the filtrate contained some factor that inhibited sulfanilamide action The antibacterial effect he attributed to the inhibition of some enzyme reaction fundamental to bacterial reproduction but not a protein substance This enzyme reaction according to Green is normally catalyzed by a substance which he has called pullulation factor P factor which is extracted from bacteria This factor was found to have in vitro a specific antagonistic action to sulfanilamide The mechanism of action thus resolves itself into a balance and whether sulfanilamide has an antibac

terial effect in such a system depends upon its greater depressing action than is the stimulating action of the P factor

Woods also of the University of London in 1940[6] isolated a similar non specific extract from yeast which he was able to purify further by chemical analysis He demonstrated a fairly constant quantitative relationship between the sulfanilamide and the inhibitor and arrived at a rather startling conclusion as to its chemical identity His studies suggested that the active factor was a substance of low molecular weight probably similar to sulfanilamide itself and that it was probably an amino derivative of an aromatic carboxylic acid In his search for such a substance the most readily available chemical to answer these specifications was p aminobenzoic acid In testing this simple chemical compound for possible antisulfonamide effects he discovered that the substance possessed such properties to an astonishing degree He found that a molecular concentration of 1 10 000 000 was active in partially inhibiting the bacteriostatic effect of sulfanilamide at a concentration of 1 20 000 Seventeen other compounds of similar chemical structure were studied and the only ones having activity in comparable molecular dilutions were procaine the ethyl ester of p aminobenzoic acid and p hydroxylaminobenzoic acid The isomers o aminobenzoic acid and m aminobenzoic acid are relatively inactive which is especially interesting in view of the fact that the corresponding isomers of p aminobenzene sulfonamide sulfanilamide also are chemotherapeutically inactive[97]

On the assumption that p aminobenzoic acid is essential for the growth of the organism Woods postulated that there was an interference on the part of sulfanilamide in the bacterial enzyme reaction involved in the utilization of this substance This interference by sulfanilamide is of the nature of a competitive inhibition due to a structural relationship existing between sulfanilamide and p aminobenzoic acid In this competitive inhibition Woods has suggested that in the enzyme reaction necessary for the utilization of p aminobenzoic acid sulfanilamide offers competition for a position in this reaction because of the similarity in their chemical structures and that if sulfanilamide is accepted taken up in the enzyme reaction growth of the cells is inhibited On the other hand if sufficient p aminobenzoic acid is present it obtains preference as a food substance for the organisms sulfanilamide is displaced and cell growth is accelerated Carrying this idea further Martin Wisansky and Ansbacher[5] observed that both sulfanilamide and p aminobenzoic acid are effective in modifying melanin formation that these two aromatic amines attack at the same point which suggests a common point of attack for the two substances in bacterial systems Contrary evidence of such

an hypothesis has been given by Rubbo and Gillespie[99] By varying the concentration of p aminobenzoic acid in a medium containing a constant amount of sulfanilamide these authors obtained results which led them to the conclusion that 'one molecule of p aminobenzoic acid antagonizes 23 000 molecules of sulfanilamide

In view of the gross disproportion between these two antagonistic substances they conclude that it is difficult to conceive how the acid growth activator can overcome the effect of the growth inhibitor sulfanilamide if the two molecules are destined toward the same receptor site on the organism Notwithstanding occasional objections the majority of investigators have accepted and confirmed Wood s observations but that is in vitro, for at the moment it is supposed that p aminobenzoic acid is an essential metabolite for bacteria but for technical reasons it has not yet been isolated from them nor has it been proved to be a growth factor in the absence of a bacterium which cannot synthesize it[100] However Fildes has shown that it antagonizes sulfanilamide action in vivo inasmuch as animals die from a streptococcal infection in the presence of a curative dose of sulfanilamide if p aminobenzoic acid has been added

Para aminobenzoic acid has been found in vitro to inhibit sulfapyridine sulfathiazole and sulfadiazine also but slightly differently under varying conditions Spink and Jermstra[101] found it inhibited all the sulfonamides with staphylococci With pneumococci the effect is less with sulfapyridine least with sulfathiazole[10] but it has no effect on the pneumococcidal antibodies in fresh defibrinated blood P aminobenzoic acid is absorbed readily after oral administration with maximum blood levels in 1 to 2 hours after ingestion Excretion is rapid and practically completed in 12 hours The drug is found in greater concentration in the plasma than in the red blood cells Some of it is present in conjugated form in the blood and urine The pneumococcidal action of human blood resulting from the administration of the sulfonamide drugs can be overcome by the ingestion of p-aminobenzoic acid

This substance being a primary arylamine couples with N (1 naphthyl) ethylenediamine dihydrochloride producing a red color It can be detected therefore in body fluids by Bratton and Marshall s method of determination for sulfanilamide However when both p aminobenzoic acid and a sulfonamide compound are present in the blood or urine it is impossible to estimate the quantity of each by this method

From the studies that have been carried out so far with this most interesting substance p aminobenzoic acid there can be said to be at least four practical applications in therapeutics

a) *Relation to vitamin B* From a theoretical point of view it is of interest to note that p aminobenzoic acid has been identified recently as a part of the vitamin B complex that fraction needed by rats to keep their hair from graying and by chicks and certain bacteria for their growth This may raise the question whether vitamin B complex should be interdicted during sulfonamide treatment As Grabfield puts it[107] in these days of indiscriminate exhibition of vitamins this may not be so absurd More studies on this subject will be awaited with interest

b) *The use of local anesthetics* A number of local anesthetics of the procaine series all of seven according to Keltch and others[104] derived from p aminobenzoic acid inhibited the action of sulfanilamide in vitro and some of them also inhibited sulfathiazole It has been observed that the use of large quantities of local anesthetic agents containing this acid grouping is contra indicated under circumstances in which interference with the action of the sulfonamide drugs is undesirable For example Boroff Cooper and Bullowa found that using 1½ c c of 2 per cent novocaine B diethylaminoethyl p aminobenzoate gave a concentration of 0 0002 per cent procaine in the pleural fluid By tests in vitro this amount definitely inhibited sulfapyridine action

c) *The culture of bacteria* As discussed under the pharmacology of these drugs when they have been administered to patients the various body fluids particularly the blood urine and spinal fluid contain relatively high concentrations of the sulfonamides and various transudates and exudates frequently contain significant amounts When cultures for organisms are made from these fluids in nutrient broth enough sulfanilamide is carried over frequently to delay or prevent the growth of organisms that may be present Hence instead of obtaining growth from a positive blood culture in 3 or 4 days an incubation of 10 to 12 days may be required Under such circumstances the addition of a small amount of p aminobenzoic acid to the nutrient medium 5 mgm per 100 c c of nutrient broth[10] will overcome this sulfonamide action and allow the full growth of any organisms in the usual growth period provided they are still viable Therefore it seems of distinct advantage to add p aminobenzoic acid routinely to all culture media in hospital laboratories

d) *Action on toxic effects* Immediately it would be suggested that if p aminobenzoic acid inhibited sulfonamide action it might by some action such as the possible tendency of sulfanilamide to hinder the combination of p aminobenzoic acid with the particular enzyme in body cells an action responsible for the utilization of this substance prevent or hasten recovery from the toxic effects of the sulfonamide compounds

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of an unsubstituted (free) sulfonamide (SO_2NH_2) or sulfonhydroxamide grouping and is completely independent of the para amino grouping Since this inhibition is related to the free SO_2NH_2 group of sulfanilamide it is not affected by sulfapyridine or sulfathiazole

Oxidation Theory — The oxidation theory may be said to have begun with Mayer[109] progressed through Scudi[110] James[111] and Schaffer[112] and has culminated at present in the beautiful correlation by Fox[84] As early as 1937 Mayer[109] suggested the possibility that an oxidation product of sulfanilamide formed within the body and not sulfanilamide itself was the substance responsible for the anti bacterial activity Oxidation products have been found in the urine but no definite evidence that any of the sulfonamide drugs undergo oxidation in the body was forth coming until 1939 when Scudi and his associates[110] reported the recovery of a urinary concentrate of diazotizable substances in a concentration con siderably above the solubility of sulfapyridine This suggested that the drug might be excreted as a sulfate or glucuronide a view supported later by the findings that a single dose of 5 gm of sulfapyridine in human subjects causes a marked increase of glucuronic acid excretion over a period of 24 hours[110] Subsequently the glucuronide of sulfathiazole and a hydroxy body probably a phenol from sulfanilamide have been iso lated in the urine James[111] has recovered p N acetyl hydroxylamino benzene sulfonamide p hydroxylaminobenzene sulfonic acid and p amino phenol products of oxidation in the body from the urine of patients treated with sulfanilamide

With this evidence of oxidation in the body the problem was attacked by Fox[84] at Columbia University but from a different viewpoint Since methemoglobin is formed so commonly in patients receiving sulfanila mide treatment since this abnormal pigment is formed from hemoglobin only by the action of strong oxidizing agents and since sulfanilamide itself is not an oxidant and does not form methemoglobin outside the body he reasoned that the administration of the drug must be accom panied by the constant formation of some substance capable of oxidizing hemoglobin to methemoglobin By a number of ingenious experiments Fox has oxidized sulfanilamide the resulting solution oxidizing hemo globin to methemoglobin with the formation of a brown solution iden tical with that identified from patients receiving the drug By producing oxidation in vitro he was able to observe elimination of the lag phase of growth reproduction of bacteriostasis by low threshold of inoculum size and supportive evidence of why sulfanilamide is so effective in septice mia i e because it is an infection in a well oxygenated environment He emphasizes however that only a particular oxidation product of

That idea has been tested and found wanting McCarty[106] observed that the acid had no effect upon the immediate fatal toxicity of sulfapyridine for mice Strauss Lowell and Finland[107] gave p aminobenzoic acid to patients who had developed fever or a skin rash from sulfonamide therapy while continuing the therapy and noticed no influence Likewise they gave the acid to patients known to be susceptible to sulfonamides administered the sulfonamides and produced a rash and fever The acid also will not explain the toxic reactions From this it may be concluded that Fildes original suggestion that p aminobenzoic might inhibit the toxic effects of the sulfonamides in human tissues has not been realized

Lockwood[27] has correlated the p aminobenzoic acid and peptone theories Although there is yet no direct evidence that the inhibitory effect of peptone and of other proteolytic products is due entirely to their content in p aminobenzoic acid or some structurally related material there is such close similarity in the nature of the antisulfanilamide effects of these substances as to suggest that the same mechanism accounts for the sulfonamide inhibiting properties of proteolytic products Hence when bacteria attempts to invade tissues in which the proteins have not yet been subjected to degradation into simpler constituents by proteolysis and the available supply of the essential metabolite is not great sulfanilamide blocks the enzymatic utilization of the traces of p aminobenzoic acid which are present having been synthesized by bacteria from primarily essential amino acids or obtained preformed from the environment and the bacterial cells are unable to proliferate

Other substances that have been found to inhibit the bacteriostatic effect of sulfanilamide besides peptone certain fractions of streptococci certain fractions of Brucella and p aminobenzoic acid include certain coenzymes (West and Coburn[107]) extracts of certain animal tissues (MacLeod[71]) extracts of mouse blood and urine and lemco Green has found that general gamma irradiation of the guinea pig completely inhibited the therapeutic activity of sulfanilamide

Carbonic Anhydrase Anti enzyme Theory — Another theory not investigated extensively which supposes interference with bacterial metabolism is that of sulfanilamide inhibition of the action of an enzyme of the body known as carbonic anhydrase[103] The function of the enzyme carbonic anhydrase in the human body is to convert metabolic or inhaled carbon dioxide into bicarbonate Inhibition of this enzyme is manifested by a decreased tolerance for inhaled carbon dioxide by patients treated with sulfanilamide This action which has been observed both in vitro and in vivo after sulfanilamide is dependent apparently upon the presence

of an unsubstituted (free) sulfonamide (SO_2NH_2) or sulfonhydroxamide grouping and is completely independent of the para amino grouping. Since this inhibition is related to the free SO NH group of sulfanilamide it is not affected by sulfapyridine or sulfathiazole.

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sulfanilamide is effective that in which the product formed is itself an oxidizing agent Reducing conditions favor bacterial growth The application of these facts to the problem is that sulfanilamide bacteriostasis probably rests upon the production of oxidizing conditions which serve to inactivate enzymes and inhibit bacterial growth that sulfanilamide bacteriostasis is nullified by reducing conditions which reactivate enzymes and favor bacterial growth

This theory of oxidation fits in well with Mellon s hypothesis already given and the two hypotheses may be correlated in still a different manner from the earlier work of Shaffer[11] It has been reported by Shaffer that the potential of the oxidation products of sulfanilamide at pH7 0 is plus 0 45V which is considerably higher than the normal potential of any other organic substance yet measured except sulfapyridine and adrenalone Since the cell in the course of its normal metabolism is protected from values higher than about 0 26V it would appear certain according to Shaffer that an oxidant with a potential of plus 0 45V would attack every reactive reducing system in the cell Among the cell components to be attacked would be the enzyme catalase According to this theory as a result of this neutralization of catalase there occurs a local accumulation of hydrogen peroxide which in the presence of ferric or ferrous ions is itself a powerful oxidant of sulfanilamide Hence oxidation products toxic to bacteria in this manner would be formed at a rate dependent upon the rate at which O_2 became available and H_2O_2 was produced Against the oxygen theory is the fact that definite bacteriostasis has been produced with sulfanilamide and sulfapyridine in anaerobic media with concentrations of less than 0 04 per cent oxygen Obviously the bacteriostatic effect of these drugs in the absence of air tends to discredit the concept that these drugs are activated by molecular oxygen

These theories have been concerned chiefly with the effect of these drugs on the bacteria The other half of the story is the part which body immunity plays in finally overcoming the infection for as already stated these drugs hold the organisms in check until body immunity overcomes the infection and the patient recovers

Host Factors in Action of Sulfonamides — Body immunity has not been found to be either stimulated or depressed However as observed thus far the immune mechanism that develops may take one of two or possibly three forms These host factors have been demonstrated experimentally chiefly in mice

In the first of these if streptococci in relatively small amounts are injected into the peritoneal cavities of mice and treatment then is begun

in 6–8 hours two things happen The first is that after two to four hours lag phase the multiplication of the cocci becomes definitely retarded this is a bacteriostatic effect Secondly with bacteriostasis there occurs an increase in phagocytosis If treatment is continued the number of extracellular cocci decreases steadily as phagocytosis increases until a point is reached when the exudate becomes free from visible streptococci If such mice are pretreated that is given an amount of the drug the day before and again an hour before the injection of streptococci and the infecting dose is large although some bacteriostasis and phagocytosis may take place the streptococci multiply rapidly and the mice succumb in 12 to 16 hours If the organisms are grown for several generations in 20 mgm per cent sulfanilamide blood broth before injection after injection both bacteriostasis and phagocytosis begin immediately and within a few hours the peritoneal exudate becomes clear of streptococci with further treatment If the animals are not treated such pretreated streptococci quickly regain their original virulence and the animal succumbs within 24 hours These findings are interpreted to indicate that the previous injection of mice with sulfanilamide does not activate the drug and that pretreatment of the streptococci makes them immediately susceptible to the effects of the drug when injected into mice which have been treated The development of antibodies does not play any part Thus in this type of host response phagocytosis seems to have an important function in finally ridding the animal of the infectious agent whereas specific antibody production either does not occur or is of minor importance

In the second type of host response the mechanism was demonstrated with pneumococci instead of streptococci If mice are pretreated with sulfapyridine and then infected with a strain of type I pneumococcus highly virulent to the mice a definite multiplication of the cocci occurs for the first four to six hours If treatments are continued a change takes place for the number of cocci rapidly decreases but with a minor degree of phagocytosis until practically none can be found in the peritoneal exudate at the end of 18 hours What happens to the cocci is not known but they are not engulfed by phagocytes Again if the pneumococci are grown for several generations in 20 mgm per cent sulfapyridine blood broth and then are injected into mice which have been pretreated and then are treated further with sulfapyridine bacteriostasis begins almost immediately the cocci disappear slowly from the exudate but phagocytosis is only slight Thus it seems that while the drug is holding the infecting organisms in check the organisms must be acting antigenically to bring about a type specific immunization of the animal

Hence in this type of response primary phagocytosis is slight and the drug exercises merely an inhibitory effect upon the infectious agent until the specific immune bodies which develop naturally are able to cope with the infection

A third type of host response has been observed in mice infected with *Clostridium* (*Bacterium*) *Welchii* and treated with sulfanilamide It was found in such experiments that without pretreatment of the organisms but with the mice treated thirty minutes before being infected the bacteriostatic effects of the drug became evident immediately There is no lag period Furthermore in the beginning phagocytosis is equal in both the control and treated mice but as time goes on less phagocytosis is noted in the treated mice obviously because there are fewer bacilli to be engulfed This represents a host response in which no bar to phagocytosis exists in either the treated or control animals this demonstrates an in vivo bacteriostatic effect In this type of response although phagocytosis is very important the primary factor in recovery seems to be the immediate bacteriostatic effects of the drug upon the invading microorganisms[113]

Drug Resistance —An interesting phenomenon that has been observed in the action of these drugs is so called drug resistance It is a phenomenon in which at first a bacteriostatic effect occurs against the organism but the infection persists For some unknown reason the organism becomes resistant to the action of the drug and unless the natural immunity overcomes the disease the patient later may die This phenomenon has been observed to occur with pneumococci gonococci colon bacilli staphylococci aurei and a few other organisms In studies of this kind carried out by numerous observers using chiefly the pneumococcus as an example it has been found that the susceptibility of different strains of pneumococci to the action of these drugs exhibit considerable variations These variations were observed in different laboratory strains isolated from different patients and in strains obtained from the same patient at different times in the course of treatment Thus drug resistant strains may occur naturally That drug resistance may be acquired has been demonstrated amply both in vitro and in vivo In vitro it can be produced by successive cultivation in media containing increasing amounts of the drugs beginning with concentrations too low to inhibit bacterial multiplication Different strains of organisms vary in the ease with which they acquire such resistance The same phenomenon has been produced in vivo by administering suboptimal bacteriostatic doses of the drug over a period of time The clinical implication of this is clear namely if doses too small are used in the treatment of an infection drug resistance

of the organism may occur What doses may be too small cannot yet be defined In studies with pneumococci[94, 114, 115] it has been observed that if the organism becomes resistant to sulfapyridine it is resistant also to sulfathiazole and to sulfamethylthiazole hence the futility of changing to either of the other drugs With drug fastness of this organism however MacLeod found associated a marked diminution in the production of H_2O_2 in cultures of the type I strain studied However the quellung or swelling phenomenon still occurred and the organisms agglutinated specifically with type I rabbit serum and showed no changes in morphology virulence or specific immunological characteristics Studies with the gonococcus have been similar forcing one to the conclusion that drug resistance must be caused by changed factors in the host and not in the organism Clinically drug resistance particularly of the pneumococcus has been demonstrated infrequently and most of the deaths have occurred in instances of serious systemic disorders of inadequate therapy or of overwhelming infection at the start of treatment

Opinion stands divided as to the permanence of drug resistance Harris and Kohn[18] formulated two types of resistance type A in which resistance induced by one drug is not carried over to other drugs this is a temporary resistance and in this group belong such organisms as *B coli* and *Staph aureus* and type B in which resistance is carried over a permanent resistance such as occurs with *Hemophilus parainfluenzae* which was found to be resistant to all drugs Pneumococcus resistance has been thought to be permanent

A laboratory test has been devised by Moore Thomas and Hoyt[117] to determine in beginning treatment of a patient whether the pneumococci are sensitive or resistant to the drug chosen to be used Sodium sulfapyridine in acacia is injected intraperitoneally into several mice and later various dilutions in saline of sputum or pus containing organisms are injected also Aspirations are done at two hourly intervals and when the control untreated mouse culture outgrows the treated specimens the organism is considered to be drug sensitive If on smear the treated and control cultures are indistinguishable the organisms are considered to be drug resistant The test may take 12 to 24 hours Another test for detecting pneumococcus resistance has been devised by Cotter and others[118] Plain blood agar plates and plates containing 10 mgm of a sulfonamide compound are seeded and incubated as usual Unchanged pneumococci will grow on the plain blood agar plate only drug resistant pneumococci will grow on both plates

In conclusion the practical principles of the mode of action of the sulfonamide drugs may be summarized somewhat as follows They are

specific drugs in their action, having a powerful effect on some bacteria and being without effect on others Those organisms not affected may be naturally resistant or may have acquired a resistance The number of organisms and the type of tissue reaction are extremely important for when large numbers of even the most sensitive bacteria are present the drugs may have little or no antibacterial action if tissue destruction with necrosis is present the drugs may be without effect An intermediate substance, probably an oxidation product of the drug is most likely the mode of action of these drugs by interfering with normal bacterial cellular metabolism It is probable that bacteriostasis rests upon the production of oxidizing conditions which serve to inactivate certain enzymes and inhibit bacterial growth Peptone and certain bacterial and yeast extracts inhibit the bacteriostatic action of these drugs Their action is essentially bacteriostatic and the natural defense mechanisms of the body have to complete the destruction of bacteria In other words the sulfonamides inhibit the growth of organisms and prevent overwhelming intoxication until immunity can be mobilized and finally bring about recovery

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PART II

Sulfanilamide

The parent drug sulfanilamide has been studied the most thoroughly and the most completely of all of these compounds With this drug we have the most accurate knowledge concerning its administration and dosage the many diseases in which it has proved its usefulness as well as the conditions in which it has been found to be of little or no benefit and the best understanding of its toxic effects In fact it is the one of the several drugs that has been tested and reported upon in the largest number of diseases For these reasons it seems unfortunate that sulfanilamide appears to be subject to obsolescence or complete discard in favor of newer products The probable explanations are the eager desire to avoid some of the toxic effects and the discovery that under certain but not all comparable circumstances some of the newer compounds have been found to be just as good However sulfanilamide still has a place in the treatment of infections due to hemolytic streptococci Ducrey bacilli certain urinary tract infections and trachoma This is witnessed further by the fact that it is given preference at least for the time being by the United States Army and Navy[10] Their committee recommends sulfanilamide as the drug of choice in meningococcic meningitis and gas bacillus infections

Methods of Administration and Dosage of Sulfanilamide

By the several routes that may be utilized in the administration of these drugs and because of variations in dosage and response in individual patients as well as variations in their diseases it can be made a clinical aphorism that *the dose of the sulfonamide compounds is the dose that cures the patient* A second dictum just as important may be stated somewhat as follows Strike hard at the start subdue the infection quickly Since there has developed less fear of the toxic reactions nevertheless still mindful of them it has been learned that attacking the infection with force with these drugs right at the beginning of treatment obtains the best results In the same category Snodgrass[71] has outlined as follows some of the common errors with these drugs which are pertinent to such a discussion (1) The sulfonamide preparations are given on insufficient clinical data This is sometimes justified particularly if the

specific drugs in their action having a powerful effect on some bacteria and being without effect on others Those organisms not affected may be naturally resistant or may have acquired a resistance The number of organisms and the type of tissue reaction are extremely important for when large numbers of even the most sensitive bacteria are present the drugs may have little or no antibacterial action if tissue destruction with necrosis is present the drugs may be without effect An intermediate substance, probably an oxidation product of the drug is most likely the mode of action of these drugs by interfering with normal bacterial cellular metabolism It is probable that bacteriostasis rests upon the production of oxidizing conditions which serve to inactivate certain enzymes and inhibit bacterial growth Peptone and certain bacterial and yeast extracts inhibit the bacteriostatic action of these drugs Their action is essentially bacteriostatic and the natural defence mechanisms of the body have to complete the destruction of bacteria In other words the sulfonamides inhibit the growth of organisms and prevent overwhelming intoxication until immunity can be mobilized and finally bring about recovery

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15) per 9 kilos (20 pounds) body weight is given at once For patient over 160 pounds the maximum dose of 8 0 gm (gr 120) is used After the initial dose a similar total may be given during the remaining twenty four hours 1 0 gm (gr 15) per 9 kilos (20 pounds) body weight divided into six equal doses the first given four hours after the initial massive dose the remainder at four hour intervals around the clock On this basis at the end of twenty eight hours the patients of 160 pounds or greater weight will have received a total of 16 0 gm (gr 240) but seldom is it necessary to give over 13 0 gm (gr 200) in the first twenty four hour period to attain a blood level of 10 to 15 mgm per cent There after 10 0 gm (gr 150) per twenty four hours usually is sufficient to maintain such a blood level in the average adult When such massive doses for rapid administration are used it is essential to check daily the blood sulfanilamide level hemoglobin red and white blood cells After the temperature has been normal for twenty four hours the dose may be cut in half If a blood level between 10 and 15 mgm per cent has been maintained for five to seven days without definite clinical response in an infection amenable ordinarily to the drug the case is to be classed as a therapeutic failure and the drug is to be stopped The risk of toxic effects with such massive doses of course is considerable

Sodium bicarbonate 0 6 to 1 0 gm (gr 10 to 15) with each dose of sulfanilamide was recommended originally to lessen the tendency to acidosis produced by the drug Whether it is necessary to give sodium bicarbonate still is a controversial question which has been discussed under Pharmacology Recently the Committee on Medical Preparedness[119] has ruled that the routine use of sodium bicarbonate is unnecessary in treatment with sulfanilamide and its derivatives Instances of alkalosis following its administration have been encountered[170]

In the average case of illness of moderate severity in which sulfanilamide is indicated a blood level of 5 to 10 mgm per cent usually is adequate to aid the host in overcoming the infection *Moderate doses* to accomplish this blood level are indicated in patients who are bed ridden or possibly ambulatory but not critically ill with infections amenable to sulfanilamide These include such conditions as urinary tract infections gonorrhea puerperal sepsis erysipelas cellulitis etc. Here the dosage should maintain a blood sulfanilamide level of 5 to 10 mgm per cent which usually is sufficient for the less virulent and less critical infections However with these same diseases if the patient is severely ill the larger dose method with higher blood levels is to be used The total daily dosage usually required for a blood level of 5 to 10 mgm per cent is 0 6 gm (gr 10) per 9 kilos (20 pounds) of body weight divided

condition appears to be one in which these drugs are effective When that s the case they may be administered for 48 to 72 hours while at the same time further studies are being carried on to clarify the diagnosis If after 72 hours there has been no satisfactory response the drug should be stopped All too frequently the drug is continued the patients are exposed to its toxic effects further investigations are delayed in determining the etiology, and the really appropriate treatment is withheld because of dependence upon the compounds that are being used (2) They are given in insufficient dosage or for too short a period of time (3) When used certain elementary precautions against toxic effects often are disregarded (4) Finally other useful therapeutic measures often are neglected

Mouth dosage of sulfanilamide is the method of choice Sulfanilamide is obtainable in tablet form 0 3 gm (gr 5) and 0 5 gm (gr 7½) mixed with an excipient for oral use In the treatment of infections in human patients the oral administration of sulfanilamide has given the best results in that the concentration in the blood can be maintained by it at a more constant level It is important to realize that this group of drugs is the only one in all therapeutics where the dose is based upon blood concentration where sound experimental observations justify a schedule of dosage and where a maintenance of a constant blood concentration over several days is attempted One cannot be certain always whether a low concentration maintained continuously in the blood is more effective than repeated rises of concentrations to high levels with much less drug present in the intervals All data indicate that the best therapeutic effect results from the maintenance of a constant blood concentration for several days However there is good evidence to show that a blood concentration which is innocuous if maintained for only a few hours may prove toxic if maintained hour after hour for several days

The dosage is dependent somewhat upon the severity of the infection *Large doses* are indicated when the patient is critically ill with an infection amenable to the drug and when it may be necessary to establish a *blood sulfanilamide level of 10 to 15 mgm per cent* *In severe* infections caused by the beta hemolytic streptococcus such as meningitis septicemia peritonitis or any type of meningococcal or Welch bacillus infection gonococcal endocarditis etc it is important to obtain as quickly as possible and often necessary to maintain a high blood level up to 15 mgm per cent When large doses are employed the plan of treatment may be instituted as follows In the first twenty four hours for patients weighing less than 160 pounds an initial dose of 1 0 gm (gr

15) per 9 kilos (20 pounds) body weight is given at once For patient over 160 pounds the maximum dose of 8 0 gm (gr 120) is used After the initial dose a similar total may be given during the remaining twenty four hours 1 0 gm (gr 15) per 9 kilos (20 pounds) body weight divided into six equal doses the first given four hours after the initial massive dose the remainder at four hour intervals around the clock On this basis at the end of twenty eight hours the patients of 160 pounds or greater weight will have received a total of 16 0 gm (gr 240) but seldom is it necessary to give over 13 0 gm (gr 200) in the first twenty four hour period to attain a blood level of 10 to 15 mgm per cent Thereafter 10 0 gm (gr 150) per twenty four hours usually is sufficient to maintain such a blood level in the average adult When such massive doses for rapid administration are used it is essential to check daily the blood sulfanilamide level hemoglobin red and white blood cells After the temperature has been normal for twenty four hours the dose may be cut in half If a blood level between 10 and 15 mgm per cent has been maintained for five to seven days without definite clinical response in an infection amenable ordinarily to the drug the case is to be classed as a therapeutic failure and the drug is to be stopped The risk of toxic effects with such massive doses of course is considerable

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into 5 equal doses over a twenty four hour period given at 8 00 A M 12 00 noon 4 00 P M 8 00 P M and 12 00 midnight The dose may be reduced twenty four hours after clinical improvement has been seen It is recommended in cases of these less critical illnesses that if no improvement is apparent within two or three days in an infection which should respond to sulfanilamide the dose be increased sufficiently to raise the blood level above 10 mgm per cent for another three to five days before abandoning the drug

Small doses are indicated in most ambulatory patients in those who do not tolerate the drug well and in those circumstances in which it is found that minimal amounts of sulfanilamide will aid satisfactorily in overcoming the infection Small doses are recommended also when it becomes necessary to administer the drug over a long period of time Ten grains (0 6 gm) four or five times a day should be given This will give a blood level of 1 to 5 mgm per cent In the ambulatory patient large doses are not to be used because it has been found that unpleasant side effects such as headache dizziness and skin eruptions are more apt to occur in persons ambulatory exposed to sunlight This and other ambulant toxic effects are discussed further under Toxic Effects

The amount of sulfanilamide per pound or kilogram of body weight required to establish adequate blood levels of the drug in infants and children up to 12 years of age is considerably greater than that needed in adults This variation is due to the fact that the fluid intake per kilogram of body weight is normally greater in young children than in adults and when fever is present this difference is even more marked[11] In children up to 12 years of age one may give 60 mgm (gr 1) per pound body weight as an initial dose followed by a similar amount every twenty four hours divided into six equal doses In infants to whom it may be difficult to give the tablets or who are in coma and where intravenous or subcutaneous administration is not practicable an 0 8 per cent solution of sulfanilamide can be given by stomach tube or indwelling nasal catheter Lowenburg[1] reports success with a palatable liquid vehicle for children The formula is as follows

Sulfanilamide	60 0–120 0
Powd tragacanth	1 20
Glycerine	5 20
Alcohol	2 0
Syr raspberry	120 0
Dist water to	180 0

Shake well for 5 minutes and give 1 teaspoonful every four to six hours

Ordinarily it is not desirable to give sulfanilamide or related compounds in a vehicle. Other vehicles are discussed under Local Use and the dangers are given under Toxic Effects.

The *parenteral administration* of sulfanilamide sometimes is desirable even necessary in the treatment of infections with this drug. If the patient cannot swallow the tablets if coma or vomiting be present or if there is reason to believe that the absorption of sulfanilamide from the gastrointestinal tract may be faulty the drug may be given parenterally. The tablet for oral use is relatively insoluble in water and is not to be used for intramuscular subcutaneous or intrathecal injection.

For *intramuscular* injection the red liquid neoprontosil may be used. This is discussed under Other Related Chemotherapeutic Agents.

For *subcutaneous administration* the pure sulfanilamide powder can be dissolved up to 0.8 to 1.0 per cent concentration in physiological saline solution. This is done by bringing 100 c.c. of the saline solution to boiling for two or three minutes adding 0.8 to 1.0 gm. (gr. 12 to 15) of the white crystalline sulfanilamide powder and shaking the flask gently until the drug has dissolved completely. This solution of the drug may be sterilized by boiling for 5 minutes or by autoclaving at 10 to 15 pounds pressure for a similar length of time. Such additional sterilization is desirable but not essential. The sulfanilamide solution then is allowed to cool to 37 C. and at this temperature it may be administered into the subcutaneous tissues under the pressure of gravity. Such an 0.8 per cent solution will remain fairly stable if kept at *room temperature*. If the solution is allowed to cool as in an icebox the chilling may bring about the precipitation of the sulfanilamide. It is best therefore to prepare the solution freshly each day. Sulfanilamide solutions that have a yellow tinge should be discarded as such a discoloration is a sign of decomposition of the drug. Sulfanilamide in 0.8 per cent solution is available on the market.

At the time it was considered important to give sodium bicarbonate along with sulfanilamide Long and Bliss recommended dissolving the powder in $\frac{1}{6}$ molar solution of sodium r lactate. A molar solution of sodium r lactate contains 18.67 gm. of the lactate compound per liter of distilled water. To make a $\frac{1}{6}$ molar solution one part of the molar sodium r lactate is added to five parts of physiological saline solution. If the lactate solution is not available one may use Hartmann's *solution* which contains sodium r lactate. It is advisable to use this mixture parenterally in patients with a deficiency of total fixed base in the body fluids.

The dosage of the 0 8 to 1 0 per cent solution of sulfanilamide for subcutaneous use has been computed according to body weight The total doses generally are larger than those given by mouth One hundred cubic centimeters are to be used for individuals weighing up to 40 pounds or 18 kilos from 40 to 80 pounds 18 to 36 kilos 200 c c from 80 to 120 pounds 36 to 72 kilos 300 c c over 120 pounds 72 kilos 400 c c A satisfactory initial dose for adults is 400 to 700 c c The initial dose for subcutaneous sulfanilamide should be one half of the total first day dose computed on the basis of the drug when given by mouth Subsequent treatments are to be given at 6 to 8 hour intervals For example if the estimated 24 hour oral dose is 10 gm for an initial parenteral injection one would give 5 gm of powder dissolved in 500 to 600 c c saline followed in 8 hours by 4 gm in 500 c c and repeated in eight hours This would make a total of 13 gm in twenty four hours slightly larger than the oral dose Since this method of administration has the advantage of supplying fluids as well as the drug to the patient it is best not to adhere too rigidly to a given dosage but to carry out treatment toward the attainment of an adequate blood level sufficient to cure the particular infection

A similar solution 0 8–1 0 per cent of sulfanilamide in saline may be given *intrathecally* in the treatment of meningitis if desired However the majority of observers now consider this route of administration unnecessary in most instances when this drug is used because an adequate level of concentration in the spinal fluid may be attained by giving the drug by mouth If one desires to give it the dose for intrathecal injection is 15 to 25 c c of the 0 8–1 0 per cent solution prepared as described above One removes first slightly more cerebrospinal fluid than the quantity of sulfanilamide solution to be injected The intraspinal injection should be made always by gravity method never under pressure

Sulfanilamide is the only one of these compounds that is absorbed at all satisfactorily from the rectum therefore it may be administered *rectally* if desired It is absorbed better in 0 8 to 1 0 per cent solution than in suppository form Seven or eight grams (105 to 120 gr) in 0 8 to 1 0 per cent solution (700 to 800 c c) over a period of 24 hours may give a blood level as high as 10 mgm per cent The dose by rectum is the same as by mouth If it is desired to use suppositories they must be inserted high into the colon to obtain best absorption of the therapeutic agent

It is never necessary or advisable to administer sulfanilamide *intravenously* It has been found that the oral or subcutaneous administration is just as effective as intravenous injection in clearing the blood stream

or spinal fluid of organisms By the intravenous route the drug is excreted so rapidly by the kidneys that a blood level of adequate concentration is difficult to maintain Furthermore untoward reactions are not uncommon after intravenous use

The *local application* of sulfanilamide is considered in a separate discussion Part VIII of this chapter

Variations in the dose and routes of administration and combinations with other drugs particularly serums and vaccines have been tried in various types of infection These will be dealt with subsequently in the consideration of the respective diseases under Other Medication Along with Sulfanilamide

Occasionally particularly during a therapeutic test with these drugs it may be desirable or necessary to change from one sulfonamide compound to another Such a change is made as a rule without difficulty As an example a patient may exhibit the clinical features of an infection due to a hemolytic streptococcus and sulfanilamide is begun Subsequent events reveal that the condition is due to a pneumococcus or a staphylococcus and it may be desired to change to sulfapyridine or to sulfathiazole In such a case the sulfanilamide is discontinued at once and the other drug begun on a maintenance dosage Because the colorimetric determination of blood level of these drugs is quite similar it may be difficult to obtain accurate blood levels of the sulfapyridine or sulfathiazole until all the sulfanilamide has been excreted Such a determination can be made usually after 24 hours and the dosage schedule of the more recently instituted drug adjusted accordingly

The question of when to stop sulfanilamide therapy may be very difficult to answer Opinions vary some advocating its withdrawal immediately upon subsidence of the fever others recommending its continuation for a week after clinical improvement is noted If the drug is withdrawn too soon relapse may occur With clinical effect the usual course of treatment is 10 to 14 days Whitby[14] has advocated that if the drug is not completely effective at the end of 14 days it is wise to give a rest period of two days in order that the body may be cleared of the drug altogether and a fresh course then instituted at the end of that time

With a background of knowledge of toxic effects recognized as being due to the drug the consensus of opinion seems to be to treat the infection energetically at the start and when the disease has been brought under control the sulfanilamide is to be decreased gradually until the patient is up and about At this period it is probably safe to discontinue its use altogether

Clinical Uses of Sulfanilamide

Animal experiments have defined clearly the specificity of these drugs and the genus and type of organism upon which they are active. Although not always comparable, ideally the human case demands a bacteriological control in order that unsuitable infections may not be submitted to prolonged treatment with a drug that is unlikely to be effective. In fact, then, the practitioner has to become necessarily a bacteriologist. Practically, however, such expert bacteriological control cannot be exercised with the facilities available to the average general practitioner. The variable factor of personal opinion as distinct from hard fact allows considerable latitude in prescribing these drugs, which latitude indeed can neither be avoided nor condemned.

On occasions, furthermore, one is confronted with a patient displaying some signs of invasive infection, but in whom a definite diagnosis cannot be made. To withhold the drug might allow the patient to die. In such cases a *therapeutic test* with one of the sulfonamide compounds is permissible and even is indicated. If no evidence of a therapeutic response is obtained within 48 to 72 hours, it is probable that further continuation of the drug will be futile and perhaps undesirable. Thus further continuation of the course of treatment, after a trial period of a few days has shown no clinical effect, can be avoided. With three days of such a therapeutic test one seldom would experience toxic reactions.

In Table II are listed the conditions in which sulfanilamide has been found to be of distinct value in promoting bacteriostasis and curing the

TABLE II

INFECTIONS IN WHICH SULFANILAMIDE IS EFFECTIVE*

Actinomycosis	Gonococcus infections
Arthritis (purulent)	*Arthritis* (acute)
Bites of venomous marine animals	Meningitis
Barracuda	*Ophthalmia neonatorum*
Catfish	Urethritis (complications)
Portuguese man of war	Vulvovaginitis
Sea urchins	Hemophilus influenzæ conjunctivitis
Brucellosis (acute)	Icterus neonatorum (due to umbilical phlebitis)
B. suis	
Chancroid	*Lymphogranuloma venereum*
Colitis, ulcerative (chronic, mild)	Meningococcus infections

* Words in italics are those conditions in which sulfanilamide is especially effective.

Septicemia
Meningitis
Pneumococcus infections
Meningitis
Pyomyositis
Streptococcus beta hemolytic infections
(Lancefield group A B C G)
Abscesses (drained)
Adenitis
Angina (Ludwig's)
Bacteremia
Cellulitis
Empyema
Endocarditis
Erysipelas
Erythema multiforme
Lymphangitis
Mastoiditis
Osteomyelitis
Otitis media
Peritonitis
Pericarditis
Peritonsillar abscess
Pharyngitis
Pneumonia
Puerperal sepsis
Scarlet fever (complications)
Septicemia
Sinusitis (acute)
Skin infections
Impetigo
Intertriginous ringworm
Pemphigus
Tracheobronchitis
Ulcer
Streptococcus viridans infections
Abscess
Cellulitis
Meningitis
Osteomyelitis
Peridental infection
Septicemia
Trachoma
Ulcer tropical
Urinary tract infections
Hemolytic streptococcus (group D)
Bacillus proteus
Hemophilus influenzae

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lesion It has been especially useful in those conditions appearing in italicized print and at the time of the present writing sulfanilamide may be said to be the drug of choice in the diseases appearing in italics As the evidence is accumulating it would appear that sulfadiazine may replace sulfanilamide under certain circumstances which will be discussed under that drug

A few of the conditions listed merit some further discussion Introduced first with its startling results in infections due to the *beta hemolytic streptococcus* the newer drugs with less toxic effects are promising to replace sulfanilamide Nevertheless its value and effectiveness is witnessed by the long list of conditions due to this organism given in Table II Although *pharyngitis* and *tonsillitis* are listed the results are not always good In *otitis media* the results may be striking but numerous observers have warned against the masking effect on the mastoid complication that this drug may have On the other hand it has reduced the incidence of *mastoiditis* from 22 7 per cent before the advent of sulfanilamide to 3 4 per cent [15] In its masking effect the x ray evidence of mastoiditis may be distorted also The reasonable attitude seems to be that when the clinical picture suggests mastoiditis operate

value once the inflammatory process in the adnexæ has become well established

Sulfanilamide has been effective in some of the complications of gonorrhea In *gonorrheal ophthalmia* particularly in children it has been more effective than any other form of therapy employed previously Corneal scarring may be prevented and the vision may be saved if the drug is administered promptly The use of the drug is helpful also in the allergic type of conjunctivitis (non purulent) frequently seen in acute gonorrhea

Although the newer compounds are replacing sulfanilamide to a large extent the value of this drug in *arthritis due to the gonococcus* has held a place The best results are obtained in the acute and subacute types It is most effective when the joint is purulent In such cases the synovial fluid can be sterilized in 48 to 72 hours after the drug has been given by mouth This is most fortunate for the cases having organisms and purulent exudate in the joint are the ones that are most apt to develop severe joint destruction On the other hand improvement with sulfanilamide therapy of chronic gonorrheal arthritis of three to four months or longer duration seldom is dramatic The drug does not hinder body immunological processes in that it does not influence the gonococcal complement fixation reaction of the blood Sulfanilamide chemotherapy often is effective in gonococcal arthritis whether the complement fixation reaction is positive or negative

From the various reports the results of sulfanilamide therapy in *vulvovaginitis in children* have been rather disappointing Although it may be effective it has not become a method of choice Some cases of *endocarditis due to the gonococcus* have recovered apparently under sulfanilamide therapy and in others its effect has been negligible It is worthy of serious trial in this condition however

In *lymphogranuloma venereum* particularly of the rectum sulfanilamide is effective in the acute or subacute stage especially if there is no stricture It produces improvement in the general condition but has no effect on a stricture Administration frequently must be prolonged

In the treatment of *streptococcic meningitis* sulfanilamide remains the drug of choice although sulfadiazine threatens to replace it but before doing so it will have to prove itself more effective than reducing the mortality rate 75 per cent In other words before sulfanilamide the mortality in *hemolytic streptococcic meningitis* was 95 to 100 per cent Since its introduction the fatality rate has dropped to about 20 to 25 per cent The best results are obtained by the administration of large doses by mouth to attain a blood level of 10 to 15 mg per cent Intrathecal

administration has been abandoned now by most clinicians as unnecessary

In *meningococcus meningitis* the results also have been very successful. Recently the Council on Chemotherapy has named sulfanilamide as the drug of choice but it would appear also that sulfadiazine will share the honors. Meningococcemia responds splendidly to chemotherapy. The drug protects equally well against strains I and II of the meningococcus. This affords a distinct advantage for sulfanilamide therapy over the use of serum alone because the latter may not contain the specific antibodies for the particular strain of organism infecting the patient. Treatment must be instituted early and in large doses. Intensive treatment particularly in meningitis has been shown to reduce the mortality from 25 to 30 per cent when treated with serum to 10 to 15 per cent when treated with sulfanilamide. When specific antiserum is available for intravenous use combined serum and sulfanilamide should be administered. Serum intrathecally is not necessary and may be even harmful. The daily oral dosage of sulfanilamide recommended for the average case is 8 to 12 gm (gr 120 to 180) to give a blood level of 10 to 15 mgm per cent. It is best to continue medication in smaller doses until the temperature has been normal for seven days.

Steele and Gottlieb[136] in an analysis of the reported cases of *pneumococcus meningitis* between 1937 and 1940 uncovered the unexpected fact that except for type III infections sulfanilamide was definitely superior to sulfapyridine in the treatment of this condition. Sulfathiazole probably is out of the question because of its inability to penetrate adequately the meninges. So until further evidence is forthcoming sulfanilamide appears to be the drug of choice in this disease.

In *pneumonia particularly due to the streptococcus* sulfanilamide can be very effective. Although sulfanilamide had been employed with promising results in *pneumococcal infections* such as pneumonia peritonitis otitis media and mastoiditis interest and experimentation has waned considerably in enthusiasm for sulfanilamide since the introduction of sulfapyridine sulfathiazole and sulfadiazine. However in a careful study of mouse infections with 47 strains of 30 types of pneumococci Schmidt and Hilles[137] found that the therapeutic effectiveness of sulfanilamide against these organisms was considerable in some case 100 per cent survivals resulted. They administered the drug every six hours day and night maintaining a blood concentration of 8 to 12 mg per cent and demonstrated that the infrequent administration of the drug was responsible for the failure of earlier observers to obtain beneficial effects clinically. There is little data on the clinical value of sulfanilamide in

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pneumococcus pneumonia because the newer drugs have established them selves However in the one careful study of its intensive use very good results are reported[1,3]

When the alpha hemolytic streptococcus *Streptococcus viridans* is not enmeshed in a blood clot as is seen in *Streptococcus viridans* endocarditis sulfanilamide can be very effective in eliminating this organism In the first place this organism is of extremely low virulence hence usually large doses of the drug are not required Secondly the drug is much more effective against the mouth group of this organism than it is against the enterococcus group Sulfanilamide is particularly effective in clearing the blood stream and frequently the urinary tract of this organism

The subjective symptoms and objective signs of *trachoma* particularly in the acute phases of the condition are much improved by oral medication with sulfanilamide Photophobia and lacrimation can be made to decrease in 24 hours Vision will improve usually even with pannus formation present It has been reported that corneal lesions respond more rapidly than do conjunctival With the treatment there is paling of the conjunctiva and trachomatous patches with flattening of granules and follicles It is not a specific treatment however as it does not help the pannus per se the keratitis or the ulcer formation The local application of sulfanilamide has promise in this condition also

Sulfanilamide was received enthusiastically and proved of great benefit in the treatment of *urinary tract infections* Effective as it has proved to be sulfanilamide is being replaced rapidly by sulfathiazole and sulfadiazine Sulfacetimide holds promise of being added to these

Originally it was considered that high urinary concentrations were necessary for effective bacteriostasis in the urine It has been held that the good results are due to the high urinary concentrations of the drug 10 to 20 times higher than those attained in the blood and to the fact that urine is a poor medium for bacterial growth More recently ample evidence has been presented that low urinary concentrations frequently produce results just as good and toxic reactions are minimized or eliminated Furthermore the limitation of fluid intake to obtain higher urinary concentrations is not essential Although it has been customary to restrict the amounts of fluids in administering sulfanilamide to adults with urinary tract infection fluid restriction in children is not advocated because of the ease with which dehydration and acidosis develop especially in infants Alkalinization with sodium bicarbonate was advocated too along with sulfanilamide and that has been found unnecessary as a routine procedure A dosage of 2 6 to 4 gm (gr 40 to 60) of sulfanilamide in divided doses over a period of 6 to 7 days usually is adequate The

blood level produced by this amount ranges from 2 5 to 6 0 mgm per cent [139]

Such a dosage with adequate diet and forced fluids is effective for the majority of organisms found in urinary tract infections It is particularly effective against group B hemolytic streptococcus and *B proteus* It even in larger doses has no effect on *Streptococcus fecalis* For *B coli* and staphylococci sulfathiazole has become the drug of choice

Sufficient experience with these drugs in the treatment of urinary tract infections has been accumulated to make possible the enumeration of several factors that make for failure (1) Acute infections respond better than chronic ones Chronic cases can be brought under control usually but there is apt to be relapse (2) It is seldom wise to continue to treat chronic infections without sufficiently complete diagnosis to indicate the presence or absence of gross disease Particularly mechanical factors such as ureteral obstruction calculus disease etc may be the cause of chronicity and of relapse in the chronic cases under treatment When such factors are removed the infection is apt to respond better to treatment (3) Something should be known of the function of the kidneys Kidney function in relation to urinary output of sulfanilamide has been discussed under Pharmacology

Cases of urinary infection on constant drainage offer little chance for sterilizing the urine as long as the drain is kept in place This is applicable particularly to prostatic hypertrophy and its surgical treatment The presence of the drainage does not prevent the tissue effect of sulfanilamide from taking place as evidenced by subsidence of temperature but does prevent the production of sterile urine Post operatively for *bladder infections after prostatectomy* Alyea and Roberts[77] have found that a delay of three weeks and then the institution of sulfanilamide produces better results than come from immediate use of sulfanilamide

Sulfanilamide is very effective in the treatment of *cystitis* as found so frequently *in women with diabetes* Very often small doses are sufficient It is with diabetes and its acidosis that the concomitant administration of sodium bicarbonate with sulfanilamide may be helpful The sulfonamide compounds do not have any effect on the diabetes per se and insulin therapy is to be carried out in the usual way Neither drug is a contraindication to the use of the other

In Table III are listed conditions in which sulfanilamide has been tried and the effects may be said to be doubtful It is expressed in this way either because of the conflicting evidence some reports claiming good results others entirely ineffective or because an insufficient number of reports of a condition have appeared to allow one to formulate a

pneumococcus pneumonia because the newer drugs have established themselves However in the one careful study of its intensive use very good results are reported[1 8]

When the alpha hemolytic streptococcus *Streptococcus viridans* is not enmeshed in a blood clot as is seen in *Streptococcus viridans* endocarditis sulfanilamide can be very effective in eliminating this organism In the first place this organism is of extremely low virulence hence usually large doses of the drug are not required Secondly the drug is much more effective against the mouth group of this organism than it is against the enterococcus group Sulfanilamide is particularly effective in clearing the blood stream and frequently the urinary tract of this organism

The subjective symptoms and objective signs of *trachoma* particularly in the acute phases of the condition are much improved by oral medication with sulfanilamide Photophobia and lacrimation can be made to decrease in 24 hours Vision will improve usually even with pannus formation present It has been reported that corneal lesions respond more rapidly than do conjunctival With the treatment there is paling of the conjunctiva and trachomatous patches with flattening of granules and follicles It is not a specific treatment however as it does not help the pannus per se the keratitis or the ulcer formation The local application of sulfanilamide has promise in this condition also

Sulfanilamide was received enthusiastically and proved of great benefit in the treatment of *urinary tract infections* Effective as it has proved to be sulfanilamide is being replaced rapidly by sulfathiazole and sulfadiazine Sulfacetimide holds promise of being added to these

Originally it was considered that high urinary concentrations were necessary for effective bacteriostasis in the urine It has been held that the good results are due to the high urinary concentrations of the drug 10 to 20 times higher than those attained in the blood and to the fact that urine is a poor medium for bacterial growth More recently ample evidence has been presented that low urinary concentrations frequently produce results just as good and toxic reactions are minimized or eliminated Furthermore the limitation of fluid intake to obtain higher urinary concentrations is not essential Although it has been customary to restrict the amounts of fluids in administering sulfanilamide to adults with urinary tract infection fluid restriction in children is not advocated because of the ease with which dehydration and acidosis develop especially in infants Alkalinization with sodium bicarbonate was advocated too along with sulfanilamide and that has been found unnecessary as a routine procedure A dosage of 2 6 to 4 gm (gr 40 to 60) of sulfanilamide in divided doses over a period of 6 to 7 days usually is adequate The

eradicate the organisms temporarily only to have the cultures become positive again after the cessation of treatment The drug has a most pronounced effect on *cellulitis of the deep structures of the throat and neck* due to the hemolytic streptococcus and its use in severe infections is justified However it fails usually to sterilize foci of latent infection in the tonsils Its indiscriminate use is to be opposed

Although successive trials with these drugs bring periodically further encouraging results in the treatment of *Streptococcus viridans endocarditis* this condition is placed in the doubtful group because the failures still outnumber the successes by a wide margin Many have been the failures reported nevertheless a review of the literature reveals nearly 50 cases reported as recovered up to the present time The unsuccessful use of sulfanilamide and related compounds in this condition is attributable to the nature of the pathological lesion namely the presence of the organisms deep in vegetations on the heart valves and the inability of sulfanilamide to penetrate such vegetations[41] Friedman[42] confirmed the inability of these drugs to penetrate blood clot and in addition performed a rather ingenious experiment By placing *Streptococcus viridans* and sulfanilamide or sulfapyridine plus *Streptococcus viridans* in capsules in the abdominal cavity the author found that if the drug was given immediately there was bacteriostasis of the organisms in the capsules On the other hand if not given immediately the organisms grew rapidly Although these drugs are not the solution of the problem the results are encouraging enough to stimulate diligent search for new chemotherapeutic agents or better application of those available for use in the treatment of bacterial endocarditis In the use of sulfanilamide in this condition the clinical response has been extremely variable It may make the colonies in the blood culture fall in number not change or rise in number It may reduce fever or cause pyrexia The patient may feel improved or no better In the majority of controlled studies the drug has seemed to make little difference in the survival time of patients with *Streptococcus viridans* endocarditis In the few cases that have recovered besides the unknown factors the survival has been attributed to doses as low as 1 gm (15 gr) daily for a long period of time[143] as well as to intensive treatment with blood levels as high as 20 to 24 mgm per cent [144]

When it was seen that sulfanilamide alone did not raise appreciably the survival rate in *Streptococcus viridans* endocarditis variously combined treatments were tried These include a sulfonamide with heparin[145] a sulfonamide with neoarsphenamine[146] and a sulfonamide combined with pyrexial therapy[147] Although not limited strictly to sulfanilamide these methods are pertinent to this discussion With heparin both sulfanila

TABLE III

INFECTIONS IN WHICH SULFANILAMIDE EFFECT IS DOUBTFUL

Colitis ulcerative acute and severe	Salmonella infections paratyphoid A B C D
Filariasis	Shigella infections
Friedlander bacillus infections	Dysentery
Gas gangrene caused by clostridia	Paradysentery
Hemophilus influenzae infections	Sonne
Meningitis	Skin diseases
Hemolytic streptococcus tonsillitis simple acute	Lupus erythematosus
Infectious mononucleosis	Pemphigus staphylococcus
Malaria	Streptococcus viridans bacterial endocarditis
Plague	Thrombophlebitis suppurative
Pneumococcus infections	
Empyema	
Pneumonia	

conclusion It is to be hoped that some of the newer compounds or the original ones in different applications or combined with other forms of treatment may make the sulfonamide compounds more useful in the doubtful conditions listed under each of the compounds and even in some of the so far unaffected diseases

In some of these conditions the newer drugs sulfathiazole and sulfadiazine are proving to be of distinct benefit They are discussed under *those drugs*

Originally sulfanilamide was heralded with success in the treatment of *gas gangrene* due to *Bacillus* (*Clostridium*) *Welchii*[140] but confirmation was lacking in fact studies in vitro and in animals disclaimed such results Recently however the local application of this drug on the battle fields of Europe has raised again hopes of beneficial results in this dreaded condition It is discussed further in Part VIII of this chapter

A word more needs to be said about the treatment of *sore throat* and other minor infections of the upper respiratory tract due to the hemolytic streptococcus The word minor is used here in the sense of a superficial mild infection Their treatment with sulfanilamide has not given good results consistently The failures far outnumber the successes and in control series[141] the clinical course was practically identical Sulfanilamide was not found to reduce the severity of the symptoms shorten the period of incapacity reduce the incidence of complications or reduce the duration of the carrier state Studies have shown that if a streptococcal sore throat is treated early by oral ingestion of the drug it may

TABLE IV

INFECTIONS IN WHICH SULFANILAMIDE IS INEFFECTIVE

Anthrax	Syphilis
Arthritis	Trichomonas vaginalis
Atrophic	Trichiniasis
Hypertrophic	Tuberculosis
Blastomycosis	Tularemia
Chorea	Typhoid fever
Diphtheria	Virus infections
Endocarditis	Chicken pox
Brucella	Common cold
Pneumococcus	Encephalitis
Phlebitis, non suppurative	Influenza
Psoriasis	Lymphocytic choriomeningitis
Rheumatic fever, acute	Measles
Rickettsial infections	Mumps
Rocky Mountain spotted fever	Poliomyelitis
Typhus fever	Psittacosis
Scarlet fever	Rabies
Sinusitis, chronic	Smallpox
Staphylococcal infections	Yaws
Streptococcal anaerobic infection	

has been found to be ineffective in the treatment of *acute rheumatic fever* or *chorea* and in the prevention of rheumatic fever by treatment of the sore throat that so frequently precedes an acute exacerbation of rheumatism. On the other hand encouraging results are being obtained in the prophylaxis of the sore throat and subsequent rheumatic fever; this is discussed under the prophylactic use of these compounds.

If sulfanilamide is used in the treatment of acute rheumatic fever it has been found that about half the cases develop a toxic rash, and in many instances the fever and leukocytosis seem to be increased. Sulfanilamide does not influence the arthritis and has no effect on the antistreptolysin titer curve which develops as if no treatment had been given.

In *staphylococcal infections* sulfanilamide ordinarily does not produce satisfactory results except in urinary tract infections. The reason is as discussed under mode of action that peptone substances inhibit the drug's effect. However in staphylococcal bacteremia and in instances where the local purulent exudate has been removed first mechanically, the drug often is quite effective. Used in conjunction with antitoxin or serum sulfanilamide may be more helpful than either agent alone.

The treponema pallidum of *syphilis* is not affected by this drug, and prontylin has had no effect on the blood serological tests for this disease.

mide and sulfapyridine have been tried at first with encouraging results particularly if the blood stream first was cleared of organisms and the heparin instituted later but subsequently with discouraging results because of frequent complications such as cerebral hemorrhage and possibly acute glomerular nephritis due to the heparin

Sulfanilamide plus neoarsphenamine in the treatment of bacterial endocarditis has not seemed as promising as the latter drug with sulfathiazole This is discussed under Sulfathiazole

Lichtman Bierman and Baehr have reported quite encouraging results with types of fever therapy and a sulfonamide The idea is promoted from the work of White[148] which showed that sulfanilamide and sulfapyridine produced better results under conditions of increased temperature even though it has been found that most strains of *Streptococcus viridans* seem able to resist temperatures as high as the human body can stand Fever therapy alone seems to increase embolization possibly as the result of increased speed of blood flow Best results come from at least eight bouts of induced fever given on alternate days with temperatures of 104–106° F maintained for five hours If typhoid vaccine is used to produce the fever at least 6 sessions on alternate days are desirable Radiation therapy along with a sulfonamide has been tried also but the results have been questionable

In an evaluation of the above combined methods it is to be recalled that spontaneous cure occurs in about four per cent of cases of *Streptococcus viridans* bacterial endocarditis With this as a base line evidence in several reports indicate that these various methods have cured more than could be explained as spontaneous cures with percentage of recoveries ranging from 6 to 25 per cent and best results claimed for the combination of chemotherapy and artificial hyperthermia So far there are not enough cases in these reports to justify a final evaluation of them with each method of treatment Because of the cardiac involvement for which this treatment is being instituted it does not seem amiss to issue a word of warning and caution particularly in the administration of physically induced pyrexia and its effect on the heart and circulation

The failure of sulfanilamide and sulfapyridine to cure pneumococcal endocarditis has been noted numerous times

In Table IV are listed the conditions in which sulfanilamide has been found to be ineffective In many of these sulfapyridine sulfathiazole and sulfadiazine have been said to be ineffective also but in several the newer drugs have been found to be useful These separate entities will be discussed under the appropriate drug

Several of these conditions may be discussed further Sulfanilamide

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Phlebitis non suppurative	Influenza
Psoriasis	Lymphocytic choriomeningitis
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In the other infectious granulomata the results have been conflicting but chiefly negative In animals a beneficial effect of sulfanilamide has been reported for *tuberculosis* but in man this has been entirely unconfirmed The hope perhaps possibility of the new drug promin in this condition is discussed under that drug

The virus diseases as a group do not respond to sulfanilamide or related compounds Their inefficacy in virus infections when compared to certain bacterial diseases may be due to the intracellular nature of the former as against the extracellular character of the latter The common cold considered to be due to a virus and an organism in symbiosis is not altered in its course In chicken pox measles and scarlet fever sulfanilamide has no effect on the disease per se but when used judiciously is very useful in the treatment of the bacterial streptococcal complications In smallpox it seems to decrease pustulation and so shorten the attack and decrease pock marks It may have prophylactic value against the complications also

Toxic Effects of Sulfanilamide

With the drugs containing the sulfonamide linkage there are certain toxic manifestations which are a denominator common to all of those that have been tried up to the present time In addition there are particular manifestations peculiar to the individual compounds With the increasing number of sulfonamide derivatives which are being presented for clinical use it becomes necessary to look for individual and even unsuspected toxic manifestations as well as the ones already recognized Because of the greater frequency of untoward effects with sulfanilamide and our better understanding of them the present section deals extensively with toxic effects the toxic manifestations peculiar to the other compounds will be considered less extensively when those drugs are discussed However a few generalizations applicable to all of them should be mentioned briefly

Important as these toxic effects are the attitude and point of view regarding them has changed somewhat as experience has been gained For example at first cyanosis with sulfanilamide was considered in discussions at great length and now is merely mentioned when sulfapyridine was first coming into its own there was no special consideration given to hematuria and now we have come to consider it a toxic manifestation of much significance We have learned too from observed clinical pictures that toxicity of these drugs in the human may be quite different from and greater than what animal studies originally led us to predict In

stead of thinking in terms of single reactions, it has been realized that several isolated effects often occur together. Because of individual variations toxic reactions cannot be predicted for a given dose. When blood levels are far in excess of usual therapeutic levels, untoward manifestations are to be expected. Among individual variations intolerance to the sulfonamides seems to be more frequent among patients in the higher social strata, such as among artists, musicians, writers, clergy, physicians, etc.

The toxic reactions resulting from these drugs are rather frequent, yet those dangerous to life are relatively uncommon. While it is advisable whenever possible to utilize laboratory control in following patients receiving sulfanilamide or its derivatives, practically all of the untoward effects can be detected by the physician at the bedside if he exercises reasonably careful clinical control over his patient. Most of the toxic manifestations occur in the first two weeks of treatment, and except for acute leukopenia, are easy of bedside recognition. Long[49] has outlined briefly bedside means of detecting the more serious toxic effects. Patients receiving these drugs for the first time should be seen at least once a day. The physician should inquire how the patient feels with special reference to headache, body aching or malaise, because these symptoms are the precursors of many of the toxic reactions. In addition to these symptoms he should examine carefully the scleræ for the presence of jaundice and the conjunctivæ for injection or paleness. Jaundiced scleræ with pale conjunctivæ suggest that an acute hemolytic anemia may be developing. If the conjunctivæ are not pale, then the jaundice probably results from liver damage. The occurrence of injected conjunctivæ and scleræ together with smarting and burning of the eyes so far has occurred as a toxic manifestation only in the course of sulfathiazole therapy. The oral mucous membrane should be looked at and inquiry made as to whether or not the patient has anything to suggest sore throat. If the patient has been treated with a sulfonamide for more than a week and while under treatment develops a moderately severe sore throat, this may indicate the beginning of agranulocytosis, because if he is being treated adequately, it would be quite unlikely that he would be getting an hemolytic streptococcal sore throat at this time. The skin of the body always should be examined in a good light for a rash. If the fever of the infection has disappeared, temperatures should continue to be taken for a time to detect the onset of toxic reactions which often are accompanied by fever, and to detect toxic fever. It is well always to have urine specimens collected in some container each 24 hour period and the quantity noted. Possible hematuria should be looked for in these specimens.

Finally it is well to remember that if a patient has ever had injection of the scleræ or conjunctivæ hepatitis acute hemolytic anemia drug fever leukopenia purpura hemorrhagica skin rash a diarrhea in the course of therapy with a sulfonamide drug he is very likely to have a second earlier and more severe toxic reaction if the drug is administered a second time

The question arises not infrequently whether the administration of these compounds will aggravate an already existing anemia leukopenia hepatitis dermatitis nephritis etc These are not aggravated unless the patient is one of those unfortunates to develop an unpredictable toxic reaction It is well to remember that elderly patients with cardiac renal or hepatic disease cannot stand larger doses with the impunity of other individuals and that the drugs must be given with caution to any patient with anemia leukopenia jaundice or impaired renal or cardiac function In final analysis the only ***contraindication to the use of these drugs*** is a previous toxic reaction

The toxic effects which occur following the administration of the sulfonamide compounds may be the result of either an idiosyncrasy to the drug on the part of the patient or to its indiscriminate use The amount of drug necessary for therapeutic response far from uniform in any given group of individuals is very important in the causation or prevention of toxic manifestations Larger and more frequent doses are being advocated from time to time as experience is being gained and fear lessened even though very often small doses are sufficient to obtain the desired results Large doses if necessary often are tolerated well However it is advisable when possible to give the minimum amount of the drug that will produce the desired results It must be remembered too that toxic symptoms are not related necessarily to the effectiveness of therapy with the drug or to its blood level

Sulfanilamide is to be given in its simple form In the present state of knowledge the use of sulfanilamide suspended in a vehicle except possibly for local use is to be deprecated One such vehicle diethylene glycol was the causative agent in many deaths[149] in all 105[150]

Certain chemical changes occurring in the body after sulfanilamide administration may have a bearing on the cause of toxic effects Early in the course of study of toxic effects particularly in relation to skin reactions Brunsting[151] demonstrated an increased porphyrin output in the urine of patients during the phase in which a skin rash appeared after exposure to sunlight These results were only suggestive however since it is a well known fact that many states of fever or infection for which sulfanilamide would be given lead to an increase in porphyrin

output Carrying these investigations further, Rimington and Hemmings[152] found an increase in coproporphyrin I and III excretion in the urine and stool of all patients and animals given sulfanilamide The increased excretion persisted for several days after the drug was discontinued These findings suggested two things (1) a disturbance in hematopoiesis or in liver function and (2) that the nausea colic vomiting muscular weakness etc which occurs following sulfanilamide therapy may be related to the increased porphyrinuria since these same symptoms are exhibited by patients suffering from acute porphyrinuria

The amount of drug conjugated in the body in the form of the acetyl salt may be important also in the causation of toxic manifestations The acetyl salt is more toxic than sulfanilamide and when administered to humans gives rise to some lowering of the CO_2 combining power of the blood[illegible] Normally the acetyl derivative is present in fairly low concentrations in the blood of patients receiving sulfanilamide but should an occasional individual acetylate much more of the drug than the average toxic symptoms might result from this cause

Toxicity experiments indicate that sulfanilamide is a substance of relatively low toxicity but by no means completely devoid of it Although as described under Pharmacology it appears to be inert in blood and tissue concentrations greater than those usually obtained in its therapeutic use large doses cause symptoms the nature of which suggest that the central nervous system mainly is affected the symptoms in the early stages of poisoning resemble those seen after large doses of ethyl alcohol those in the later stages are similar in many respects to the symptoms shown by decorticated animals

The toxic manifestations of sulfanilamide may be classified as mild moderate and severe Patients exhibiting mild symptoms usually complain of general malaise, anorexia headache tinnitus vertigo and nausea they may show slight cyanosis and dyspnea The dizziness nausea headache excitement or confusion occurring as mild symptoms are thought to be cerebral in origin The moderately severe effects may be classed as a progression of any of the foregoing symptoms with special reference to acidosis cyanosis and dyspnea which may prove distressing to the patient for an extended period of time Acidosis and cyanosis are considered to be direct toxic effects The severe reactions may result in the formation of a persistent sulfhemoglobinemia numbness and tingling of the hands and feet skin manifestations neuritis abdominal pains diarrhea hyper or hypo pyrexia severe disturbances in the acid base equilibrium chest pains tachycardia which may be paroxysmal and persistent dyspnea Leukopenia agranulocytosis hemolytic crises jaun

dice and various other occasional manifestations may occur The fever skin reactions hemolytic anemia and agranulocytosis probably are the result of idiosyncrasy Crises following the severe toxic effects may result in collapse and even death The more serious effects of sulfanilamide are related to the skin liver bone marrow and blood An analysis of deaths has shown that most of the fatalities have been due to either severe hemolytic anemia granulopenia or toxic hepatitis Some of the symptoms in mild form chiefly fever dyspnea cyanosis and skin rashes are important chiefly because they indicate varying degrees of intolerance to the drug and therefore serve as warning signals of impending danger They are of themselves not a cause of death

A definite temporal relationship in the occurrence of certain of the toxic manifestations of sulfanilamide has been pointed out by Keefer[153] Acute hemolytic anemia when it occurs usually appears before the seventh day after treatment is begun Skin eruptions and fever usually occur between the seventh and tenth day and agranulocytosis between the fourteenth and twenty first day after treatment To put it in another way during the first week cyanosis nausea vomiting and acute hemolytic anemia may occur During the second week of therapy one must be on the alert for the development of fever skin eruptions or toxic hepatitis During the third week agranulocytosis or a chronic progressive anemia may develop

Cyanosis and dyspnea perhaps are the most common and also the least harmful toxic results of the administration of sulfanilamide It has been believed by most investigators that methemoglobin sulfhemoglobin and a peculiar red cell binding pigment in the blood are important factors in these conditions In a review of this subject Harris and Michel[154] found that in 476 patients 58 per cent developed methemoglobinemia and about 8 per cent sulfhemoglobinemia The concentration of methemoglobin is on an average proportional to the concentration of sulfanilamide and of hemoglobin in the blood Most patients who have a blood level of sulfanilamide over 4 mgm per cent have some cyanosis Cyanosis increases with a rising blood level of sulfanilamide so that with 16 mgm per cent or more 100 per cent of patients have cyanosis

Cyanosis may appear early in the use of the drug The whole blood arterial or venous has a chocolate brownish tinge When aerated it gains oxygen in normal amounts but does not become bright red it remains dark On analysis the oxygen saturation of arterial blood does not seem to be at a point low enough to explain the marked cyanosis that may occur Often the amounts of methemoglobin and sulfhemoglobin found are too small to account for the intensity of the cyanosis

Harris believes that the formation by the tissues of an oxidizing agent from sulfanilamide adequately explains the methemoglobinemia The exact chemical changes so far are unknown The action of light seems to be an important factor for as mentioned in the work of Fox under mode of action of these drugs he was able to produce methemoglobin in vitro by oxidation and an ultraviolet lamp

Methemoglobin can be determined spectroscopically yielding a band at a wave length of 630 mu Usually it is transient in character disappearing in one to three days and no lasting effects have been ascribed to it The presence of sulfhemoglobin on the other hand demonstrated by Colebrook and Kenny[145] is more apt to occur following prolonged use of the drug is of a more lasting character and may be responsible for some of the symptoms and pathological changes encountered Sulfhemoglobin yields a band in the absorption spectrum at 620 mu According to Fuller[146] sulfhemoglobin in the blood is caused by the action of oxidation products of sulfanilamide on hemoglobin in the presence of sulfides If sulfides are absent methemoglobin results Fuller advances the hypothesis that the sulfides are those present in the gut from the action of bacteria on sulfur containing food chiefly animal protein Yet many observations have shown that practically there is no evidence that dietetic precautions have reduced the occurrence of cyanosis On the other hand saline cathartics such as magnesium sulfate are to be avoided However other sulfates such as morphine codeine ferrous sulfate in usual therapeutic doses possibly because so little is given have not been found deleterious in this connection

In certain instances patients on sulfanilamide therapy may develop an acidosis This has been discussed under Pharmacology If it occurs it is more apt to follow sulfanilamide than the other sulfonamides The suppression of carbonic anhydrase by a free sulfonamide group has been suggested as the most recent explanation of the cause of acidosis

Anemia may result following sulfanilamide administration Two types of anemia are produced an acute and a chronic form Most patients taking the drug for any length of time develop a decrease of hemoglobin and red blood cells This is the slowly developing *chronic anemia* Small doses of sulfanilamide over a short period of time ordinarily cause no essential change in hemoglobin or red or white blood cell content of the peripheral blood There has been evidence presented to suggest that mild doses may act as a stimulus to the bone marrow with a resulting rise in reticulocytes

Acute hemolytic anemia has been reported fairly frequently curiously almost exclusively after sulfanilamide It is rare compared to the chronic form Such an acute anemia when it develops does so usually within

the first week after the drug has been started and the maximal anemia generally develops within three days after the hemolytic process is initiated By virtue of its rapid onset it is reasonable to believe that this form of anemia is due to an idiosyncrasy or peculiar susceptibility to the drug rather than to the administration of toxic doses Ham and Castle[17] and Gilligan and Kapnick[18] have demonstrated an increased fragility of red blood cells during the very acute phase of the hemolysis However the red blood cells that remain in the circulating blood are normal to a fragility test In a comprehensive study of this subject Fox and Ottenberg[19] have demonstrated by photoelectric spectrophotometry that the blood serum after acute hemolysis contains more methemoglobin than is present in the remaining intact red blood cells suggesting the possibility that it was the red blood cells containing methemoglobin which underwent hemolysis From their study it was not certain how much of the methemoglobin in the serum was present in the red blood cells before hemolysis some may have been formed after hemolysis by an unknown oxidant With the hemolysis the serum contains three blood pigments hemoglobin methemoglobin and a constituent known as Fairley s methemalbumin the latter being formed readily in the plasma from extracorpuscular hemoglobin This last yields a band in the absorption spectrum between 610 and 640 mu When hemolytic anemia occurs as much as thirty per cent of the blood volume may be hemolyzed yet quantitative data on the plasma and urine hemoglobin indicate that the hemoglobin that gave rise to the hemoglobinemia and the occasional hemoglobinuria represented only a very small amount of the total hemolysis However the urine contains large amounts of methemoglobin 44 to 83 per cent and there is an increased urinary and fecal excretion of urobilin During the process the blood plasma may be very dark almost black Once the hemolysis sets in it tends to continue its course even after the blood and tissues are free of sulfanilamide The anemia is accompanied frequently by a leukocytosis with white blood cell counts that may go as high as 30 000 to 50 000 There is usually an associated rise in temperature

An interesting observation has been made which suggests that negroes may be more susceptible to the development of acute hemolytic anemia after sulfanilamide than whites In a series of 47 collected cases of this condition 32 or 68 per cent were negroes[160] Six more cases in negroes have been observed since that report The reason or the mechanism of this has not been established Inasmuch as many negroes are treated with this drug this observation suggests that considerable caution should be exercised in the use of sulfanilamide in them

The effect of sulfanilamide on *the number of leukocytes* is extremely variable Whereas with the red blood cells the effect of the drug is chiefly in the peripheral circulation with the white blood cells the toxic effects take place chiefly in the bone marrow Generally it is one of depression particularly of polymorphonuclear neutrophils although a marked stimulation may occur which may or may not be preceded by a moderate decrease In granulocytopenia from sulfanilamide the bone marrow shows maturation arrest of the myeloid series with stem cell hyperplasia and absence of more mature cells[161] Agranulocytosis may occur as a toxic manifestation and may persist for a long period of time Usually it does not develop before the fourteenth to sixteenth day after the beginning of treatment and if death occurs it usually does so within two or three days after the onset of the agranulocytosis An initial low white count does not contraindicate necessarily the use of the drug as is seen in undulant fever where usually there is no change in white cells after sulfanilamide In a review of reported cases of agranulocytosis following sulfanilamide administration it has been noted that in every instance a large amount of the drug had been given before the agranulocytosis made its appearance[16] Furthermore readministration of the drug to patients who have had a leukopenia develop after the return of leukocytes to normal does not result necessarily in a reproduction of the leukopenia These observations seem to indicate that the mechanism of granulopoietic depression after sulfanilamide therapy may be different from that following the administration of such drugs as amidopyrine with which agranulocytosis may occur after the ingestion of a single dose The cause of agranulocytosis after sulfanilamide has been attributed to the benzene ring structure of the sulfanilamide molecule

Hyperpyrexia may occur during therapy with sulfanilamide Known also as drug fever it occurs in about 10 per cent of adult patients taking this drug it occurs also commonly with sulfathiazole but not with the others It is rare in children It may be difficult to ascertain to what degree the fever is due to the infection present and to what degree it is due to the drug itself Usually however when due to the drug it begins abruptly after the patient has had a normal temperature for a day or two and ceases soon after the drug is stopped It may occur at any time Lockwood Coburn and Stokinger[163] have attempted to classify the febrile responses due to sulfanilamide into three types The most common is with a slowly rising temperature occuring after the fourth day of therapy progressing daily to a level as high as 105° to 106° F and falling twenty four hours after the drug has been stopped The second a smaller group develop high fever and chills within twenty

the first week after the drug has been started and the maximal anemia generally develops within three days after the hemolytic process is initiated By virtue of its rapid onset it is reasonable to believe that this form of anemia is due to an idiosyncrasy or peculiar susceptibility to the drug rather than to the administration of toxic doses Ham and Castle[157] and Gilligan and Kapnick[158] have demonstrated an increased fragility of red blood cells during the very acute phase of the hemolysis However the red blood cells that remain in the circulating blood are normal to a fragility test In a comprehensive study of this subject Fox and Ottenberg[159] have demonstrated by photoelectric spectrophotometry that the blood serum after acute hemolysis contains more methemoglobin than is present in the remaining intact red blood cells suggesting the possibility that it was the red blood cells containing methemoglobin which underwent hemolysis From their study it was not certain how much of the methemoglobin in the serum was present in the red blood cells before hemolysis some may have been formed after hemolysis by an unknown oxidant With the hemolysis the serum contains three blood pigments hemoglobin methemoglobin and a constituent known as Fairley s methemalbumin the latter being formed readily in the plasma from extracorpuscular hemoglobin This last yields a band in the absorption spectrum between 610 and 640 mu When hemolytic anemia occurs as much as thirty per cent of the blood volume may be hemolyzed yet quantitative data on the plasma and urine hemoglobin indicate that the hemoglobin that gave rise to the hemoglobinemia and the occasional hemoglobinuria represented only a very small amount of the total hemolysis However the urine contains large amounts of methemoglobin 44 to 83 per cent and there is an increased urinary and fecal excretion of urobilin During the process the blood plasma may be very dark almost black Once the hemolysis sets in it tends to continue its course even after the blood and tissues are free of sulfanilamide The anemia is accompanied frequently by a leukocytosis with white blood cell counts that may go as high as 30 000 to 50 000 There is usually an associated rise in temperature

An interesting observation has been made which suggests that negroes may be more susceptible to the development of acute hemolytic anemia after sulfanilamide than whites In a series of 47 collected cases of this condition 32 or 68 per cent were negroes[160] Six more cases in negroes have been observed since that report The reason or the mechanism of this has not been established Inasmuch as many negroes are treated with this drug this observation suggests that considerable caution should be exercised in the use of sulfanilamide in them

These same authors in a review of all reported cases of dermatitis after sulfanilamide have attempted to construct a natural history of the eruption which emphasizes the prodromal fever, the occasional occurrence of splenomegaly, the presence of increased capillary fragility and occasional arthritic phenomena if administration of the drug is continued. Thompson[167] has pointed out that if sulfanilamide is prescribed for children with acute respiratory and other infections it may lead to difficulties in the differential diagnosis of the exanthemata, for the usual time of onset of these drug eruptions is between eight and twelve days. He states that it should be noted that this average interval falls within the incubation periods of the common infectious fevers.

Acquired hypersensitivity to the drug has been reported many times; in fact a reaction occurring as late as two years after the original administration[168] has been reported. Ordinarily in testing patients for sensitivity to the drug in hypersensitive patients, scratch, patch and intradermal tests of the skin with sulfanilamide are negative. There have been a few instances in which hypersensitive patients have shown positive homologous skin tests. The phenomenon of photosensitization in many of these cases is established and there is evidence for an allergic mechanism[169]. Experiments using the serums of hypersensitive patients have been negative, no matter whether the antigen was a saline solution of sulfanilamide or an azoprotein (sulfanilamide combined with a protein such as human serum or egg albumin)[170]. Finally, Loveman and Simon[164] state that positive skin tests may be obtained in certain cases if the patch test is applied on an area of the skin involved previously in a sulfanilamide eruption.

When compared with sulfapyridine and sulfathiazole, as discussed under those drugs, sulfanilamide rarely ever has a detrimental effect on the *kidneys* or *urinary tract*. The drug and its conjugated acetyl salt are excreted freely by the kidneys with a slight to moderate increase in the pH of the urine. Under usual conditions sulfanilamide causes an increase in the twenty-four hour volume of the urine, a marked increase in the excretion of sodium and potassium but no appreciable change in the quantity of free ammonia or in the excretion of chlorides, inorganic phosphates or total nitrogen[171]. A slight depression of renal function may occur with large doses of the drug, but this usually is transient. These changes do no harm, but with renal impairment as in acute nephritis marked azotemia with uremia and death may result following sulfanilamide, even though several have advocated the use of this drug in acute nephritis, presumably because of its etiological association with streptococcal infections.

four hours after treatment is started The third group consists of cases with previous sulfanilamide intolerance which on subsequent administration show a hypersensitive reaction with chills aches a spiking temperature to 104° F headache and leukocytosis as high as 30 000 within six hours This third group can be prevented by giving a test dose of 0 3 gm (gr 5) of the drug and recording the temperature frequently for 12 hours If a rise in temperature or untoward effects do not appear it is safe generally to readminister or to continue sulfanilamide therapy The symptoms of hyperpyrexia may resemble serum sickness and eosinophilia may be present It has been found that fever often is the forerunner of more serious toxic effects such as acute hemolytic anemia agranulocytosis hepatitis and dermatitis Thus fever caused by sulfanilamide therapy often constitutes an important warning signal of more serious toxic manifestations

Various and bizarre types of *skin rashes* occur occasionally with intolerance to sulfanilamide There is no single rash characteristic of the drug and there is no lymphadenitis accompanying it The types of cutaneous reactions that have been reported include morbilliform eruption dermatitis from photosensitization erythema multiforme scarlatiniform eruption fixed eruption (i e the pigmented areas left by the active stage of some of the rashes) stomatitis urticaria purpura varioloform eruption and exfoliative dermatitis One instance of transient alopecia[164] and one of erythema nodosum following sulfanilamide[16] have been reported Erythema nodosum is more common with sulfathiazole and is discussed under that drug

The sulfanilamide rash occurs principally over the face back buttocks and flexor surfaces of the extremities It may occur over the entire body or it may be confined to the extremities There may or may not be associated fever and pruritis There is some evidence to show that persons sensitive to local anesthetics and those who have had other drug rashes are more likely to be sensitive to sulfanilamide

The rash frequently but not necessarily is related to direct exposure of the skin to sunlight or to ultraviolet light Therefore patients on large doses of these drugs and ambulatory patients had best avoid these sources of light Frequently twenty four to forty-eight hours before the eruption develops the urine may become deep orange or slate colored due to the increased excretion of porphyrins The opinion held generally is that the leukocytic picture during the sulfanilamide rash shows either no change or a polymorphonuclear leukocytosis Schlesinger and Mitchell[166] determined that if patients developing a skin rash are followed closely a leukopenia may develop following an initial leukocytosis

A few *other complications* such as erosion of the oral mucosa transient nodal rhythm of the heart hiccough splenomegaly and myopia have been attributed to sulfanilamide Baker[177] has reported an instance of ball shaped tufty hemorrhages occurring along the smaller arterioles in the fundi of the eye along with macular hemorrhages and a normal appearance of the remaining vessels The blood pressure and blood picture in this patient were entirely normal The fundi here resembled changes due to a blood disturbance such as leukemia Such complications are quite rare and they usually clear up with cessation of the drug

Treatment of Toxic Manifestations of Sulfanilamide — The antidote for sulfanilamide intoxication is water of which large quantities should be administered to free the patient of the drug Nothing needs to be done for mild cyanosis If there develops severe oxygen want by the production of too much methemoglobin and the consequent danger of tissue damage or death the intravenous injection of isotonic glucose solutions immediately reduces the methemoglobin to hemoglobin thereby permitting the blood to carry oxygen again and relieving the symptoms[178] For mild nausea the administration of the tablets after meals or in milk or gruel or the administration of oxygen may be helpful in preventing this unpleasant symptom

In all instances in which moderate or severe complications arise the first step in treatment is to discontinue the use of the drug Should cyanosis become severe or be accompanied by dyspnea further use of the drug is interdicted Bed rest and forcing of fluids are of much value in relieving the majority of the symptoms A diuresis causes an increased rate of excretion of both free and conjugated sulfanilamide although the increase is not proportional to the increase in the formation of urine It has been mentioned that the symptoms of nausea colic constipation and muscular weakness of acute porphyrinuria may be similar to the symptoms seen in patients taking sulfanilamide who excrete excess porphyrin in the urine

On this basis as in the treatment of pellagrins with their porphyrinuria McGinty Lewis and Holtzclaw[179] gave nicotinic acid in 50 mgm doses to negroes who were taking sulfanilamide and noted considerable improvement of mild toxic symptoms particularly of mental apathy Nicotinic acid has been used extensively with varying results in the treatment of the mild symptoms of sulfanilamide toxicity In the writer's experience the benefits have been far from striking Sodium bicarbonate and sodium r lactate has been useful in combating the lowered plasma CO combining power of the blood that may occur The administration

More severe toxic *neurological manifestations* may occur than the common dizziness headache and tinnitus mentioned previously There may develop excitement confusion and *frank psychosis* In a case reported by Higgins[17] that of a female of 34 with subacute pelvic inflammatory disease there developed on three occasions a month apart following the use of sulfanilamide motor aphasia agraphia and stammering Alcohol increases the cerebral manifestations of sulfanilamide toxicity and its use should be discouraged in anyone taking these drugs particularly when driving an automobile Sulfanilamide has been found also to lower an aviator s ceiling by about 5 000 feet Because of this it is recommended that passengers and more particularly members of the crew of an aircraft should be warned against taking sulfonamide compounds within a few days of flying Other preparations such as disulon uleron and sulfamethylthiazole have been the cause of numerous cases of *peripheral neuritis* which may result in permanent paralysis a feature that has kept these drugs off the market Peripheral neuritis after sulfanilamide is very rare Single instances of involvement of the lower extremities have been recorded and Bucy has described a case of toxic *optic neuritis* following sulfanilamide[173]

Toxic *hepatitis* with jaundice may occur as an untoward reaction A subclinical hepatitis without obvious jaundice appears to be more common after sulfanilamide than has been suspected In a group of 111 patients with urinary tract infections under treatment with this drug 49 5 per cent had evidence of definite liver injury when submitted to the Van den Bergh test Only 10 of the 111 patients 9 0 per cent, exhibited clinical jaundice The hepatitis occurred both in patients with and without evidence of preexisting biliary or hepatic disease The previous existence of liver damage or jaundice requires caution in the administration of sulfanilamide but is not necessarily a contraindication to sulfonamide therapy Liver damage the result of an infection amenable to sulfanilamide may respond promptly to the drug *Acute yellow atrophy of the liver* has been reported following sulfanilamide

Sulfanilamide has been found in the placenta and umbilical cord of the human fetus[174] It may cause toxic symptoms to the infant if not administered carefully to the mother during pregnancy From experiments on rats it is suggested that a combination of sulfanilamide and barbiturates before anesthesia may be unwise in humans[175] Marks has reported[176] serious side effects when deep x ray therapy and sulfanilamide have been combined in the treatment of patients Furthermore since deep roentgen therapy often causes anorexia nausea and vomiting this may augment the same symptoms if caused by sulfanilamide

Other Medication Along with Sulfanilamide

That the administration of magnesium sulfate with sulfanilamide may cause sulfhemoglobinemia has been discussed hence magnesium sulfate either as a cathartic or as a local application is not to be used while sulfanilamide is being given For catharsis cascara mineral oil or enemata are recommended If other drugs are indicated in the treatment of the patient such as morphine codeine aspirin digitalis iron salts etc they may be given concurrently but not in combination with sulfanilamide without fear of deleterious effects Intravenous saline and glucose may be used as needed but are not to be forced unless to overcome toxic effects because of the tendency to increase sulfanilamide excretion by the kidneys

Long[151] states that it is probably a good thing to maintain an adequate vitamin intake in patients who are acutely or chronically ill with an infection for which sulfanilamide or one of its derivatives is being given He recommends the following dosage each day vitamin A 6000 I U thiamin chloride 3 mgm riboflavin 3 mgm nicotinic acid 50 mgm ascorbic acid 100 mgm and vitamin D 100-200 I U

The relation of anesthetic drugs to sulfanilamide has been studied by Adriani[17] The anesthetic action of ether and chloroform was found to be the same in normal animals and those receiving sulfanilamide When an amount of barbiturates such as amytal nembutal etc necessary to induce anesthesia was administered to rats if the animals were receiving sulfanilamide they died whereas normal controls emerged from the anesthetic state unharmed Furthermore an amount of barbiturates which induced only subanesthetic states in normal rats caused deep anesthesia and in some instances death in rats receiving sulfanilamide The implications of such a study are obvious yet very few untoward results in humans have been reported Ottenberg[18*] reports the instance of a man of 26 who was treated with sulfanilamide for left otitis media and mastoiditis A mastoidectomy later under avertin anesthesia was followed in two weeks by jaundice and acute yellow atrophy of the liver Although no conclusions were drawn the author suggests that it would seem wise in the future when patients have received one known hepatotoxic drug to refrain from the use of an hepatotoxic anesthesia

The deleterious effects which may follow the use of deep x ray therapy plus sulfanilamide have been mentioned under the toxic effects of sulfanilamide In experiments on mice Flocks Fellowes and Kerr[153] concluded that combined sulfanilamide and x ray for staphylococcal infections

of sodium bicarbonate may be necessary if appreciable amounts of total fixed base have been lost from the body fluids

In cases in which occur hemoglobin complexes (methemoglobin sulf hemoglobin etc) which cannot carry on the required oxygenation of the blood the administration of oxygen may aid in increasing the oxygen tension Cyanosis may not disappear with its use however When cyanosis is present in appreciable amounts due to methemoglobinemia it can be controlled usually by the oral administration of six doses of 0 06 gm (gr 1) of methylene blue in children weighing up to 50 pounds and six doses of 85 mgm (gr 1¼) in patients weighing over 50 pounds The intravenous route of administration of methylene blue is not recommended because of the dangers attached Methylene blue has no effect on sulphemoglobinemia

Repeated transfusions of whole blood are of considerable benefit in the treatment of either a pathological hemoglobin condition or of an anemia The effects of liver and iron in the treatment of the acute disturbances of the blood due to sulfanilamide intoxication are unknown Transfusion is indicated in the treatment of acute hemolytic anemia when the hemoglobin falls below 50 per cent or the red blood cells below 3 500 000 In addition it has been advised to keep the urine alkaline to facilitate the excretion of free hemoglobin by the kidneys Hemolytic anemia can result in death but prompt treatment by transfusion will bring about recovery in most instances

In chronic low grade anemias which frequently develop during prolonged use of sulfanilamide stopping the drug and giving iron will cause usually a prompt return of the blood to normal In fact in this type anemia can be controlled sometimes by the administration of ferrous sulfate while sulfanilamide still is being administered[180] It has been suggested that injections of yellow bone marrow may be effective in the treatment of leukopenia and agranulocytosis The dosage advocated is 50 to 100 of the 0 2 gm (gr 3) capsules daily until a monocytosis occurs The monocytosis should be followed by an increase in leukocytes A dose of 5 capsules daily then is continued until the white cell count returns to normal after which it is recommended to continue with 10 to 15 capsules daily for several weeks more The results claimed for this form of treatment have not been confirmed Intramuscular injections of liver extract may be used too in treatment with benefit

The use of thiamin chloride vitamin B_1 in large doses has been advocated in the treatment of the peripheral neuropathies which may follow the use of such compounds as disulon and uleron

PART III

Sulfapyridine

As soon as sulfapyridine was introduced extensive studies were carried out in vitro and it was found that the drug was an effective chemo therapeutic agent in the treatment of experimental streptococcic pneumococcic meningococcic staphylococcic Friedlander s bacillary and Welch bacillary infections in mice Long s earliest studies[18] demonstrated that in mice sulfapyridine was about as efficient as sulfanilamide in the treat ment of experimental streptococcic meningococcic and Welch bacillary infections and somewhat superior to sulfanilamide in the treatment of experimental pneumococcic staphylococcic and Friedlander s bacillary infections Clinically it was heralded particularly for the treatment of pneumococcic and staphylococcic infections and it was found to be useful also in gonococcic and meningococcic infections With further trial it was found to be a very useful drug for the treatment of various infections as listed in Table V The most convincing evidence has been in respect to its use in pneumococcal infections particularly pneumonia both lobar and bronchial the latter when due to the pneumococcus

Methods of Administration and Dosage of Sulfapyridine

Sulfapyridine under most circumstances is to be administered pref erably by mouth It is marketed in 0 5 gm (7½ gr) tablets 0 25 gm (3¾ gr) capsules and 0 375 gm (5 gr) enteric coated tablets For parenteral use the monohydrate sodium sulfapyridine is obtainable and for local or parenteral administration the crystalline form is available

Groups of patients of various ages receiving equivalent amounts of sulfapyridine according to their weights have on the average approxi mately the same levels of free drug in the blood stream but the individual patients constituting these groups vary widely in their blood levels so that it becomes necessary to adjust the dosage of any given case to reach the blood level desired

The dosage and mode of administration varies somewhat with the nature of the infection for which it is being given as with sulfanilamide In severe infections such as pneumococcus pneumonia and staphylococcus infection in which the patient is critically ill the absorption by mouth may be too slow and a high blood level may be necessary quickly In such instances one may administer 4 0 gm (60 gr) by mouth as an

were less effective than either treatment alone Further it has been observed that catastrophes may occur following the use of intravenous diodrast in intravenous pyelography in patients with a high blood level of sulfanilamide This is related to the medication and not to the x ray exposure

Lloyd[133] has advised that no sulfonamide should be given at the same time as organic compounds of arsenic or gold In patients suffering from both gonorrhea and syphilis he recommends that treatment of the syphilis with neoarsphenamine should be delayed until after chemotherapy with sulfonamides If both are fresh infections in view of the infectiousness of syphilis and the absence of any effect of sulfanilamide upon it such a delay of arsenical treatment may be dangerous Again each patient must be treated as an individual case and the two drugs can be given concurrently without untoward results (Schnitker) Massie[134] feels it is inadvisable to administer a sulfonamide and thiocyanate at the same time

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Although a technique for the *rectal administration* of sodium sulfapyridine has been presented this method is not recommended for the salt is irritating to the rectal mucosa and very little of it is absorbed A procedure that has been used[133] is the suspension of 6 0 gm (gr 90) of the salt with 1 0 gm (gr 15) sodium bicarbonate in 90 c c water given as a retention enema Doses of 2 to 3 gm of this may be repeated at four hour intervals By this method about three times the usual oral dose is required to obtain a comparable blood level

Several attempts have been made to use sulfapyridine combined with glucose *glucose sulfapyridine* for more effective treatment of pneumonia A 10 per cent solution of sulfapyridine in 50 per cent glucose may be given orally but as discussed under sulfapyridine in pneumonia the results with it are not as good as with sulfapyridine alone Given intravenously only a low blood level of free sulfapyridine is attained and glucose sulfapyridine is not absorbed well from the rectum

Clinical Uses of Sulfapyridine

Clinically sulfapyridine was heralded immediately in the treatment of pneumonia The results in pneumococcal pneumonia were no less than spectacular The results in gonococcal staphylococcal and certain meningococcal infections were so much better than with sulfanilamide that choice of the drugs for different infections soon became obvious Time is necessary for dissemination of knowledge of the proper use of these drugs and just as the practitioner had gotten the feel of how to use these drugs properly sulfathiazole and sulfadiazine made their appearance with a resulting certain confusion Now at least with many of these infections sulfathiazole and sulfadiazine are replacing almost completely the original two drugs Except for certain toxic effects discussed further on sulfapyridine may be said to be a very effective drug and to deserve its proper place in chemotherapy This is evidenced by the impressionable list of diseases in which this drug is effective as shown in Table V In those conditions appearing in italics it deserves preferential consideration

In the treatment of *pneumococcal infections* particularly pneumonia for which sulfapyridine was introduced the drug has produced the best results Most is known about this drug in its application to pneumonia and even though sulfathiazole and sulfadiazine seem to be replacing it one should not omit from such a discussion the many interesting facts that have been gleaned from its clinical use Since the effectivity of the two drugs sulfapyridine and sulfathiazole in pneumonia is approxi

be administered with a blood transfusion or intravenous injections of glucose or saline The intravenous route of administration may be used alone or as a supplement to oral therapy particularly when a higher level of concentration in the blood is desired

Experimentally sodium sulfapyridine has been found to be highly irritant to the stomach when given to animals orally but again results in animals do not apply always to man for Bullowa and his associates[191] have found the sodium salt to be well tolerated by mouth with better absorption and higher blood concentrations than with sulfapyridine The writer has confirmed this in several instances and has found in addition that it seems also to cause less nausea and vomiting Not only did the New York investigators find a higher blood level but by mouth sodium sulfapyridine gave blood concentrations nearly as high as with intravenous sodium sulfapyridine Using an initial dose of 5 0 gm (75 gr) by mouth a blood level of free sulfapyridine of 4 5 to 8 0 mgm per cent was present within 2½ hours and such a level could be maintained by subsequent doses of 1 gm (gr 15) every four hours

Sodium sulfapyridine has been used also for *subcutaneous injections* It is to be made up in 0 3 to 0 7 per cent solution in physiological saline Saline is preferred to Ringer s solution because of resulting turbidity of the solution with the latter The technique of preparation outlined by Taplin Jacox and Howland[illegible] is very similar to that for sulfanilamide A liter of physiological sodium chloride solution is brought to a boil and allowed to cool for 5 minutes Then 3 0 to 7 0 gm (gr 45 to 105) of sodium sulfapyridine are added the solution is allowed to cool to body temperature and given subcutaneously at a rate of 200 to 300 c c an hour Despite the alkalinity of the solution no local reactions occur This procedure is said to give a blood level of 4 to 10 mgm per cent, maintained from 18 to 36 hours Hence a single injection of 1 000 c c is to be given at 24 to 36 hour intervals depending upon the response of the patient and the blood level desired

Another method of administration of sodium sulfapyridine that has been found acceptable is the *intramuscular injection* Here a 33⅓ per cent solution is used This must be given intramuscularly and not subcutaneously Even though this solution is highly alkaline when given carefully into the deep muscular tissues there is only a slight local reaction and the absorption is satisfactory A satisfactory scheme for adults is 4 to 6 injections of 3 c c at 4 hour intervals followed by smaller doses when feasible and oral therapy if possible This mode of treatment however is not to be recommended unless to supplement or to substitute for oral administration

organism As a result today one speaks of pneumococcal streptococcal or virus pneumonia adding secondarily whether the involvement is bronchial or lobar This changing point of view is every bit as important as the chemotherapeutic drugs for it has given rise to a better understanding of the disease and to much better treatment In retrospect it was the only approach that would allow a correct evaluation of chemotherapy of serum and other therapy in pneumonia for that matter

It follows naturally that the proper treatment of pneumonia in the first place is proper diagnosis This requires besides the physical examination a careful examination of the sputum and a blood culture The advent of the Neufeld test has facilitated greatly the rapid identification of the type of invading pneumococcus Of the more than 32 known types sulfapyridine is effective against nearly all of them but there are differences in response for different strains The effect of these drugs on the pneumococcus is a reduction in their production of carbohydrate substance and a rapid clearing of them from the blood stream In fact up to the present time no instances of pneumococcus pneumonia have been reported in which there has been a recurrence of bacteremia once the blood stream was cleared of organisms by chemotherapy unless a complication such as bacterial endocarditis or meningitis was present Hence a recurrence of bacteremia indicates a severe complication The blood stream can be sterilized almost always within 24 hours if the initial colony count is below 100 and sometimes can be sterilized when the colony count is as high as 1 000 per c c

Sulfapyridine under certain circumstances has caused changes in the capsules of pneumococci an experimental fact which has led to considerable controversy and a certain amount of confusion Originally pneumococci were injected intraperitoneally into test animals and after sulfapyridine therapy it was found difficult to type the organisms[194] A little later Hilles and Schmidt[19] isolated decapsulated pneumococci (22 types) from mice treated with sulfapyridine These data led to the impression that pneumococci from human sputum cannot be typed after treatment has been started with sulfapyridine Finland has explained this[196] on the basis of too much confidence in the Neufeld method among laboratory workers and reports of no pneumococci or pneumococci no type based too frequently on cursory inspection of wet preparations of sputum with diagnostic rabbit serum Ample evidence has been presented since then to show that certain morphological characteristics of the pneumococcus producible in test tubes or laboratory animals do not occur so strikingly or regularly in human infections Since numerous observers have reported normal swelling of capsules in human infections even daily

TABLE X

INFECTIONS IN WHICH SULFAPYRIDINE IS EFFECTIVE*

Bacillus coli	Pneumococcal infection
Beta hemolytic streptococci	*Bacteremia*
(Lancefield A, B, C and G)	*Mastoiditis*
Bacillus proteus	*Meningitis*
Bacillus pyocyaneus	*Otitis media*
Dengue fever	*Peritonitis*
Friedlander's bacillus (type 1)	*Pneumonia*
Gonococcal infections	Sinusitis (acute)
Arthritis	Staphylococcal infection
Conjunctivitis	Arthritis
Endocarditis	Bacteremia
Female gonorrhea	Furuncles
Male gonorrhea	*Meningitis*
Ophthalmia neonatorum	Osteomyelitis
Vulvovaginitis	Pneumonia
Meningococcal infection	Tetanus
Bacteremia	Trachoma
Meningitis	Urinary tract infections

* Words in italics are those conditions in which sulfapyridine is especially effective.

match the same and since more knowledge is available concerning sulfapyridine the discussion of the treatment of pneumonia will be divided between these two drugs and certain differences will be considered under sulfathiazole. Most of the facts presented are common to both drugs. Although the toxic features of nausea and vomiting are a distinct disadvantage for sulfapyridine over sulfathiazole, sulfapyridine has in its favor the fact that it causes a more rapid defervescence and drug fever, dermatitis and renal complications are slightly less frequent with it than with sulfathiazole. As evidence accumulates, sulfathiazole is being found to give rise to sensitivity with severe toxic manifestations upon later administration of the drug; this is not so apt to occur with sulfapyridine.

The *treatment of pneumonia* has been revolutionized in the past four years with a reduction from an average mortality of 25 to 30 per cent to one of 6 to 10 per cent, first by the introduction of rabbit serum in 1937, then by sulfapyridine in 1938 and sulfathiazole in 1939, but this is only one phase of the subject. For whereas for many years pneumonia had been classified on the basis of involvement as bronchial or lobar with most attention on the type of pathological process present, since about 1935 and particularly since the advent of chemotherapy with the sulfonamide compounds emphasis has been placed upon the invading

On these regimes for sulfapyridine alone approximately 65 per cent of cases respond satisfactorily The usual defervescence is a prompt fall in temperature in 24 to 48 hours frequently more striking with sulfapyridine than with sulfathiazole The explanation of this is not clear unless it be due to the non specific antipyretic effect of sulfapyridine However the signs in the chest may not change appreciably In fact no immediate change in the physical signs is to be expected for the evolution of the pathological process in the consolidated area runs its usual course There may be even a temporary increase in the signs of consolidation The pulse becomes slower and less bounding the respiration slower and more normal At this stage the patient no longer seems critically ill but he may remain toxic and uncomfortable The color may be poor and he may be restless The toxic effects of the drug may be manifest The temperature may fall by a crisis like drop or by lysis The drug however frequently does not produce the characteristic changes seen during a typical crisis in pneumonia whether the crisis occurs without serum treatment or is one induced by horse or rabbit specific serum sulfapyridine may produce results more similar to a short course of bronchopneumonia

It has been estimated that the annual death rate from pneumonia in the United States is about 130 000 and if the figures on sulfapyridine given below are any index the new mortality rate should be below 40 000 In a review that the writer has made of 50 different series which comprises a total of about 25 000 (24 566) cases of pneumococcic pneumonia treated with sulfapyridine the average mortality rate was 8 87 per cent with figures as low as 0 per cent (a series of 33 cases) to a mortality as high as 23 5 per cent (81 cases in old age) For bacteremic cases the rate was 24 1 per cent The deaths that still are encountered occur mainly in elderly persons the most important factor in patients with complicating severe systemic disease and in those in whom treatment is delayed until the patient is already moribund or until metastatic infections have become established The preceding discrepancies in the mortality among the individual reports are attributable to differences in the frequency with which these factors are encountered and taken into consideration This is discussed further under prognosis That is not the whole picture For most interesting is the changing trend in mortality that has occurred since the introduction of chemotherapy in pneumonia In 1939 during the first year after sulfapyridine was introduced the average mortality rate was 6 to 8 per cent That level still is being achieved in some series In 1940 in several reports mortality began to rise slightly 10 to 12 per cent In 1941 numerous

for as long as 8 days of sulfapyridine therapy it is more reasonable to assume that the difficulties in the typing of sputum from drug treated patients are the result of a decline in the number of the susceptible encapsulated pneumococci and that this in turn is due to the bacteriostatic and bactericidal action of the drug This is as it should be for finding large numbers of encapsulated organisms after treatment means either that the drug has failed to act on that particular strain or that the treatment has been inadequate The latter is the usual explanation

The sputum having been typed the causative organism identified as pneumoccocus and blood cultures taken sulfapyridine or its sodium salt is administered immediately To the adult patient severely ill probably with bacteremia sodium sulfapyridine is to be given intravenously as the initial therapy as outlined in the previous section followed by 1 gm (15 gr) orally at 4 hourly intervals If the oral administration cannot be carried out the sodium salt may be continued intravenously subcutaneously or intramuscularly Usually in the treatment of pneumonia the drug is administered by mouth giving an initial 2 gm (30 gr) followed by 1 gm (15 gr) every four hours Several modifications of this have been tried particularly in the initial doses such as 1 gm (15 gr) every hour for four hours then 1 gm every four hours or 2 gm at once repeated in two hours then 1 gm four hourly Such variations make little difference the advantage being that some patients have difficulty in taking 8 tablets at one time The ultimate goal is the attainment of a blood level of 4 to 8 mgm per cent The total amount of the drug required in the course of the average case of pneumococcus pneumonia is 20 to 25 gm (300 to 375 gr) The auxiliary treatment for pneumonia including jackets adequate fluids oxygen and good nursing care should be carried out in the usual way

In infants and children the recommended dosage is as follows, for infants one to three months of age an effective dose is 0 15 gm (gr 2¼) every four hours for infants six months to 1 year 0 3 gm (gr 5) every four hours for children two years old 0 3 gm (gr 5) every three hours for children *five to ten years old 0 6 gm (gr 10)* every four hours and at puberty 1 0 gm (gr 15) every four hours

In an interesting study Platt[197] used a single dose method of administering sulfapyridine to children For the uncomplicated case he gave 0 3 gm (gr 5) per kilogram of body weight in one dose for the following reasons it is simpler it interferes less with the child s rest and sleep during the time he is most ill and so he is less demanding on the nursing staff and it decreases the incidence of the common toxic effect nausea and vomiting

shown recently[18] that these last cases have a poor prognosis and even worse in the presence of bacteremia

Another problem in combined serum chemotherapy is that of the development of immunity in the patient whether he needs antibodies supplied in the form of serum or if serum has been given whether he has had enough or needs more The several methods that have been promoted for the detection of immunological response are the Sabin agglutination test the mouse protective titer and the Francis polysaccharide skin test These have not proved as satisfactory as was hoped since as Robertson and his associates[19] demonstrated a few years ago in the normal course of pneumococcic pneumonia there is no linear relationship between the appearance of immune substances and recovery in other words in the normal course of pneumonia immune substances may appear either some time before or a considerable while after clinical recovery Agglutinins appear more promptly and in the highest percentage in those cases treated with sulfapyridine and serum In those treated with sulfapyridine and antigen (vaccine) agglutinins develop to a less degree than in those treated with sulfapyridine and serum but definitely to a greater degree than in those treated with sulfapyridine alone[20] In patients treated with sulfapyridine type specific antibodies develop at about the same time in the disease as in similar patients who recover spontaneously The time when such antibodies appear as in the spontaneous case is independent of the crisis when induced by sulfapyridine The exception to this is in infections due to type III pneumococcus for here the immune response is not stimulated to the same degree as in other types of pneumococci in fact it may be delayed for some time after clinical recovery has occurred

Tests for the presence of agglutinins in the patient s blood serum are not difficult to perform but they are unreliable as a measure of dosage of serum treatment alone or with sulfapyridine The mouse protective titer test is technically more difficult and also not wholly satisfactory The Francis test on the other hand may be a useful guide to serum dosage However it is too crude to detect low titer of antibody developed by most patients with pneumococcus pneumonia Hence the titer of type specific antibody must be considerable before the skin test is positive and where no antibodies have been added by giving serum the skin tests may remain negative even where there are sufficient antibodies present for recovery A negative skin test in a patient treated with sulfapyridine does not forecast death on the other hand a positive reaction is far more significant and is of value prognostically It serves as a guide for the limitation of further therapy

series are recorded with a mortality of 15 to 18 and even 20 per cent It is of interest to speculate why this should be so but the probable reasons are several Perhaps the disease is more severe but that is unlikely Possibly the drugs are not being used to their fullest extent The answer lies probably in the report of Stable at the American Medical Association in June 1941 of 15 000 cases collected from the state of Pennsylvania (9 195 treated with sulfapyridine) exclusive of the medical centers with a mortality rate of 8 95 per cent In contrast the majority of significantly large reports come from medical centers where the mortality rate is not falling further and actually is rising This means probably that more patients are being treated in the home and only the severely ill are being sent into the hospital For in charity hospitals where all are admitted the mortality has remained below 10 per cent and is continuing to drop For these reasons the mortality in hospitals probably will not drop significantly further in the near future

One attempt to reduce the mortality further has been with the combined use of sulfapyridine and serum Serum alone has produced results as good statistically as chemotherapy but has the disadvantages of cost specificity (mixed infections occur in 8 5 per cent of cases) difficult procurement ineffectiveness late in the disease and prohibition in serum sensitive or asthmatic patients Its distinct advantage is its immunity building properties With horse serum 1923 to 1938 before rabbit serum the mortality was 10 8 per cent Since 1938 the average mortality differing of course according to type of organism of 5 series with rabbit serum was approximately 5 per cent It was hoped that combining serum with its antibody content in aiding immunity with chemotherapy with its bacteriostatic action would bring even better results The first reports were very encouraging in the hope of lower mortality, but the later communications particularly when both forms of therapy were used routinely have not been any better than either alone However there are circumstances in the pneumonia patient when serum treatment in addition to sulfapyridine is advisable even necessary These include for the most part cases with the worst prognosis such as (1) with bacteremia particularly after the age of 50 (2) where the treatment has been started late in the disease (3) where more than one lobe is involved particularly in elderly patients (4) most cases over 60 years of age who have more than a mild infection (5) severe cases of type II III or V pneumococcus infection (6) all cases which do not show a proper response to chemotherapy alone in 24 to 36 hours (7) all cases which do not tolerate sulfapyridine well (8) probably in those patients in whom a capsular polysaccharide can be detected in the blood stream It has been

In *infants and children with pneumonia* even more dramatic responses have been obtained with sulfapyridine than in adults. In a series of about 700 cases in 14 different series reviewed by the writer the average mortality was 2.9 per cent, with many series having no fatalities. However, it is important to remember that in children, particularly with lobar pneumonia, the mortality rate generally is much lower than in adults. For example, in 537 cases from the Philadelphia General Hospital over a period of 6 years with no specific treatment Holmes and his associates[93] found the mortality rate of lobar pneumonia to be 1.5 per cent. Nevertheless sulfapyridine is very effective therapy and in children under 12 is to be given on the basis of 1 gr. per pound of body weight per 24 hours. The same blood levels as in adults should result. Sulfapyridine is well taken when mixed with sugar sweetened fruit juices, applesauce or jelly.

As encouraging as the results of treatment of pneumonia have been with *sulfapyridine and sulfathiazole experience has taught that there are certain definite contra indications to their use in this disease*. These include (1) marked nausea and vomiting particularly frequent with sulfapyridine, (2) erythematous drug rash, (3) hematuria and abdominal pain, (4) rapidly progressive anemia, (5) jaundice, (6) renal disease with nitrogen retention, (7) hepatic disease, (8) pneumonia developing after an abdominal operation where vomiting might cause serious trouble, (9) previous toxic reactions to these drugs and (10) leukopenia. The presence of leukopenia does not contraindicate always the administration of sulfapyridine, for when lobar pneumonia is associated with leukopenia the mortality frequently is high and the use of these drugs may be especially indicated, but they must be used with caution.

Although the *prognosis in pneumonia* has improved considerably since the advent of chemotherapy, there has been and there will remain an irreducible minimal mortality rate. Upon analysis this rate has been found to be about the same as known previously but more strikingly evident. Perhaps the greatest single factor is age, the mortality rising abruptly in individuals over 40 (15.4 per cent.) as against 3.5 per cent under 40.

The second factor and one which hopefully can be controlled by lay education is that of the time treatment is begun. If treatment is started within the first four days the average mortality is about 5.5 per cent, rising to 18.4 per cent after the fourth day. As before the type of infection remains an important factor, the mortality being highest with type III pneumococcus infections (20 per cent.) as compared with type II (10 per cent.) and type I (6 to 8 per cent.). The reason for this is

In the technique of performing the Francis skin test a 1:10,000 dilution in physiological saline of pneumococcus capsular polysaccharide (SSS), of the type homologous with that causing the pneumonia is used. From 0.05 to 0.1 c.c., containing from 0.005 to 0.01 mgm. of the polysaccharide is injected intradermally into the surface of the forearm. When so used, it is essential to carry out a control test with the same material before any serum is given. A positive skin test after serum may be used as evidence for adequate dosage only when the control test has given no reaction. The site of each injection is observed after fifteen and again after thirty minutes. When divided doses of serum have been given, the test is repeated thirty minutes before the projected dose, and further injections of serum are given as long as the test remains negative. The test is regarded as positive in the presence of a firm, edematous wheal with surrounding erythema and frequently with pseudopodia. If a test is doubtful it is best to give more serum. It is to be remembered that a positive skin test is observed occasionally in certain cases complicated by pneumococcal empyema, meningitis or endocarditis, in which further chemotherapy may be indicated.

One other circumstance may occur in which serum is to be used in addition, actually in place of the sulfonamides. This refers to the presence of *drug resistant* strains of pneumococci causing the infection. As already discussed under mode of action, certain drug resistant strains of organisms may occur naturally, particularly among certain strains recently classified as type 33, or drug resistance may be acquired by inadequate, suboptimal treatment of pneumococcal infections with these drugs. As previously brought out, when drug resistance occurs with the pneumococcus the organism is resistant to all three drugs, sulfapyridine, sulfathiazole and sulfamethylthiazole. The clinical implication is clear, namely, when drug resistance occurs it is futile to change from sulfapyridine to sulfathiazole or vice versa, and it is best, when possible, to use serum therapy.

A combination of sulfapyridine and glucose, glucose sulfapyridine, has been tried in the treatment of pneumococcal pneumonia in the hope of obviating toxic nausea and vomiting, and of obtaining better absorption so as to reach higher blood levels. Although the idea seemed rational[91, 92] the therapeutic results have been no better, for the compound is absorbed actually more slowly than sulfapyridine alone, and the resulting blood level is no higher. Given intravenously, a high blood level does result with glucose sulfapyridine but it drops rapidly. Glucose sulfapyridine is less effective in bacteremic cases; consequently from the foregoing it is not recommended as a routine preparation for the treatment of pneumococcal pneumonia.

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due to the invasive capacity of the different types and the amount of specific soluble substance which they produce The soluble specific substance (SSS) combines with and inhibits the action of antibodies for the homologous type the larger the amount of SSS present the more pronounced is the inhibition of antibody action Types I II and III in the order named produce increasing amounts of this substance and the case fatality rates are increased correspondingly The fourth factor is the presence of bacteremia which occurs in 10 to 15 per cent of cases this makes up about 40 per cent of a fatal series Although positive blood cultures are always to be regarded seriously the time of development intensity persistence of bacteremia and the colony count are to be taken into consideration Whereas before chemotherapy the mortality rate in cases with bacteremia was 60 to 75 per cent without specific treatment and 32 to 45 per cent with serum depending upon the type organism the sulfonamides have reduced the rate to approximately 25 per cent Frisch of Detroit has shown another factor of importance in evaluating chemotherapy in prognosis It has to do with the number of pneumococci present in the sputum He has found that when there are over 65 extracellular encapsulated diplococci per oil immersion field the mortality rate is high regardless of the type of pneumococcus and the form of therapy When there are less than 10 organisms per oil immersion field the patient will recover almost always even though no specific therapy is used Intermediate cases usually will recover if proper specific therapy is given This method of sputum examination is of value in following the course of the patient as well as in outlining the treatment

It is quite likely that in the future we will see an increase in sequelæ of pneumonia and pneumococcus bacteremia the sequelæ that will occur in that group of patients who formerly would have died These include empyema meningitis and endocarditis which occur in about 6 per cent of cases Empyema can be treated successfully with a favorable outcome if it is recognized promptly and the proper surgical measures taken In pneumococcus meningitis sulfanilamide or sulfapyridine at present are the drugs of choice for sulfathiazole does not penetrate adequately the meninges In this complication time has not allowed for sufficient data on sulfadiazine In pneumococcic endocarditis the result is almost always fatal regardless of which drug or form of therapy is used

Recently a new factor in prognosis has been introduced by Bullowa and his associates namely the presence of free polysaccharide in the blood stream The polysaccharide may not be toxic per se, for it may be

detected in the blood of recovered patients. Its presence seems to be a serious omen when there is bacteremia, when the adverse effects are dependent probably upon the simultaneous presence of multiplying pneumococci. In this circumstance sulfapyridine alone or even with specific serum may not cure the patient. It remains for further observations to determine whether or not a greater reduction in mortality of pneumococcal pneumonias or other pneumococcal infections may be accomplished by the inclusion of this laboratory criterion as a guide to therapy.

Finally and very important in prognosis is the presence of associated diseases, particularly heart disease, cancer, cerebral hemorrhage, active tuberculosis, etc. In Flippin's series of 800 cases[704] the immediate mortality rate of pneumonia with carcinoma and cerebral hemorrhage was 100 per cent, with active pulmonary tuberculosis 33.3 per cent and with heart disease 31 per cent.

The only ones of these eight prognostic factors that seem controllable by earlier and more intensive therapy are the second, namely, the time the treatment is begun, and possibly the sixth, the presence of complications. All the others constitute an irreducible minimum.

With chemotherapy attempts have been made to compare the sulfonamide drugs with hydroxyethylapocupreine hydrochloride in the treatment of pneumococcus pneumonia. According to MacLachlan and his coworkers[705] the two chemicals are very much alike in their therapeutic action and the cupreine derivative can be used when sulfapyridine causes too much vomiting or when drug resistance occurs with the sulfonamides. Now that sulfathiazole is replacing sulfapyridine because of the nausea and vomiting due to the latter drug, it is doubtful whether hydroxyethlapocupreine will ever be used very extensively in the treatment of pneumonia. Studies in vitro[706] on the combined bacteriostatic activity upon pneumococci of sulfapyridine or sulfathiazole and hydroxyethylapocupreine hydrochloride failed to reveal any synergistic effects of these drugs.

Sulfapyridine has been employed with some degree of success, better in some than in others, in many forms of pneumococcal infections including *otitis media*, *mastoiditis*, *peritonitis* and *meningitis*. The best results have been obtained in the treatment of ear infections using doses similar to those employed in pneumococcus pneumonia. In peritonitis due to the pneumococcus sulfapyridine may be effective orally, but better results are being obtained by the local application of the drug. This is discussed subsequently in Part VIII of this chapter.

The mortality in *pneumococcus meningitis* remains very high, 53 per cent in Hodes' series[707] and 100 per cent in Plummer's series.[708] When combined type specific rabbit serum and chemotherapy are used, the

mortality is reduced to about 35 per cent This depends somewhat on age for in Steele and Gottlieb s series the mortality rate was 100 per cent for patients under two years of age regardless of form of therapy Sulfapyridine is effective but sulfanilamide appears to be the drug of choice since sulfathiazole does not penetrate the meninges adequately On account of the high mortality rate it may be advisable when using sulfapyridine to begin with the sodium salt intravenously followed by an oral dose of 6 to 12 gm (gr 90 to 180) per day In young children the oral dose should be 1 to 3 gm (gr 15 to 45) per twenty four hours

For *lung abscess* directly following pneumococcal pneumonia and in which the suppuration presumably is due at least in part to the pneumococcus sulfapyridine should be given early It is doubtful whether this drug will have any effect on a lung abscess once it is fully developed

In the treatment of *gonorrhea* sulfapyridine soon showed itself to be considerably superior to sulfanilamide increasing the cure rate from about 60 per cent for sulfanilamide to 90 per cent for sulfapyridine in acute cases and to 80 per cent in chronic cases It was found to be effective also in bringing about cure in approximately 75 per cent of individuals in which sulfanilamide had been ineffective Further as compared with sulfanilamide sulfapyridine does not appear to produce the high incidence of subclinical asymptomatic carriers Although sulfapyridine is superior to sulfanilamide sulfathiazole has become the drug par excellence in the treatment of gonorrhea This will be discussed under that drug

After the advent of sulfapyridine in the treatment of infections it became evident that with the gonococcus a similar train of events was occurring as with the pneumococcus namely drug resistance As with the pneumococcus it was found that drug resistant strains of the gonococcus occurred naturally or could be developed acquired in cultures by beginning with subnormal doses of the drug and gradually increasing the concentration in the medium Unlike the pneumococcus when this occurred the organism was not resistant to sulfanilamide or to sulfathiazole so frequently hence there is a place for each of these drugs in the treatment of this disease when a strain of organism is encountered which is drug resistant to one of them This phenomenon of drug resistance does not cause any alterations of biological characteristics except resistance to the particular chemical compound

In the treatment of gonorrhea with sulfapyridine it has been found that often the dose cannot be as large or increased as in the case of sulfanilamide because of toxic effects Various methods of dosage have been recommended A dose of 3 gm (45 gr) a day is given for 10 to 14

days then if the urethral discharge is not stopped within 3 days the dosage is increased to 4 gm (gr 60) daily A common routine is to give the drug by mouth 3 0 gm (gr 45) daily for 5 days then 2 0 gm (gr 30) daily for an additional 5 days If the infection still is present at the end of 10 days 2 gm is continued for four more days but no treatment should be given after 14 days Sulfapyridine may be used if sulfathiazole or sulfadiazine have failed Blood concentrations of sulfapyridine of 2 to 4 mgm per cent usually are adequate and such a blood level will not be altered appreciably by fluid intakes up to 5 000 c c a day[209] Restriction of fluid therefore is not necessary and may be harmful if there is impaired renal function Concomitant urethral irrigations do not appear to be necessary although advocated by some In *gonococcal conjunctivitis* sulfapyridine is very effective Sulfathiazole is becoming the drug of choice in the therapy of *arthritis* due to this organism In the *treatment of vulvovaginitis* in childhood sulfapyridine by mouth is of outstanding value The same is true of *ophthalmia neonatorum*

The original reports on *B Friedlander* were promising of good effects of sulfapyridine in this infection but on more careful study it has been found that the good effects which actually are not striking are limited to type A infections and in type B infections the mortality has been found to be higher after sulfapyridine (83 per cent) than in untreated cases (50 per cent)[211] Since it has been known for some time that type B strains of Friedlander bacilli are immunologically related to type II pneumococci these authors have recommended the use of type II antipneumococcus serum as specific therapy instead of chemotherapy for type B Friedlander pneumonia

In *meningococcal infections* particularly septicemia without meningitis the results may be very good especially with the use of the sodium salt In a series of 900 cases reported by Ferry[212] which were treated with sodium sulfapyridine without serum as outlined by the British War Office the mortality rate was 6 to 7 per cent Such figures are a bit unusual however for other reports from the British Isles show 32 per cent mortality for sulfapyridine alone 26 per cent for sulfapyridine combined with serum and the best results with sulfapyridine combined with antitoxin In meningococcic meningitis better results are attained with supplemented therapy with serum or antitoxin Although it is apparent that sulfapyridine is effective against meningococci it has not been demonstrated that the drug is significantly superior to sulfanilamide Since sulfapyridine may be the more toxic agent preference probably should be given to sulfanilamide

Sulfathiazole has become the preferred drug in the treatment of *staphylococcal infections* but because the meninges are a barrier to it sulfapyridine is the drug of choice in *staphylococcal meningitis*. Like sulfanilamide the hemolytic skin necrotizing and lethal factors in staphylococcal toxin apparently are not affected by sulfapyridine.

Trachoma has been found to respond in many instances to sulfapyridine even better than to sulfanilamide. The reason is thought to be the maintenance of a more maintained high blood level of sulfapyridine. MacCallan[13] has voiced the opinion that the good results reported in trachoma from the sulfonamide compounds have been procured by the elimination of superimposed bacterial infections. Good results in this disease may be obtained by the intramuscular injection of 2 to 5 gm (gr 30 to 75) of sulfapyridine in a 10 per cent suspension in olive oil containing 2 per cent ethyl amino benzoate, the amount used depending upon the weight of the patient. This will give a blood level of 2.0 to 2.5 mgm per cent for as long as 10 to 14 days so that an injection need be given only every 7 to 10 days. Intramuscular administration may give rise to pain and fever.

In the treatment of *urinary tract infections* sulfapyridine gives results about equal to sulfanilamide. It does not cause an alkaline urine as does sulfanilamide and the bactericidal effect of sulfapyridine in the urine seems to depend even less on the pH than does that of sulfanilamide. It is ineffective also against *Streptococcus fecalis*. In some instances of urinary tract infection sulfapyridine may be ineffective presumably due to the presence of excessively large amounts of the acetyl derivative in the urine. The complications of hematuria, renal calculi and azotemia following sulfapyridine therapy have been mentioned and demand caution in the use of this drug in the treatment of infections of the urinary

TABLE VI

INFECTIONS IN WHICH SULFAPYRIDINE EFFECT IS DOUBTFUL

Actinomycosis	Meningitis
Anthrax	Leukemia
Bacillary dysentery	Lymphatic
Beri beri	Listerella infections
Brucella infections	Lymphogranuloma venereum
Chancroid	Streptococcus viridans bacterial endocarditis
Clostridium oedematiens maligni	Tetanus
Dermatitis herpetiformis	Ulcerative colitis
Hemophilus influenzae infections	
Bacteremia	

tract This is considered subsequently under toxic effects of sulfapyridine and sulfathiazole One may begin treatment by the use of 3 0 gm (45 gr) daily although 1 5 to 2 0 gm (gr 20 to 30) daily in divided doses by mouth often are equally as good For infants sulfapyridine in doses of 0 5 to 1 0 gm (gr 7½ to 15) daily appears to be tolerated satisfactorily

Table VI similar to the ones under sulfanilamide and sulfathiazole has been drawn up to show diseases in which sulfapyridine has been tried but conclusive evidence of good effect found wanting Bonnar[14] has reported good results with this drug in two cases of *anthrax* and Earle claims that sulfapyridine given along with large doses of vitamin B_1 appeared to produce better results in *beri beri* than the vitamin alone particularly in infants but in both of these diseases further favorable evidence has not been presented

In experimental *brucellosis* in mice sulfapyridine has been more toxic than sulfanilamide but in humans it has seemed to hold more promise than sulfanilamide It is most effective against *Br abortus* with blood concentrations of 4 to 6 mgm per cent

Probably because of its decreased solubility sulfapyridine has met with some degree of success in the treatment of bacillary dysentery particularly in children In one of the reports[1] it is only fair to add that paregoric was used also It may be used in 6 divided doses for twenty four hours on the basis of 1 gr per kilogram body weight Sulfaguanidine no doubt will become the drug of choice in this disease

An interesting observation that certainly warrants further study is that of the effect of this drug on *lymphatic leukemia*[16] The observation was an incidental one in which a man of 70 with chronic lymphatic leukemia developed pneumonia and was treated with sulfapyridine Although he had received 1 000 r of roentgen therapy for the leukemia with the institution of sulfapyridine the white blood cell count dropped from 250 000 to 7 100 Whereupon six other cases of leukemia were treated with sulfapyridine and four of them showed a rapid fall in white cell count in 14 to 18 hours The glands increased first in size then decreased The entire effect was transitory In three cases of myelogenous leukemia sulfapyridine had no effect

The effect of sulfapyridine on *Streptococcus viridans endocarditis* is discussed also under sulfanilamide Sulfapyridine was used as the drug of choice in a series of 41 cases of which 23 received heparin with four recoveries[217] In this series heparin alone was without effect on the outcome of the disease further in this study heparin did not seem to be a factor in the causation of cerebral vascular accidents With chemotherapy in this disease the type of response falls into one of three cate

gories (1) patients on whose infection the drug has no apparent effect the blood cultures remaining positive and the temperature elevated in spite of high blood concentrations (2) patients whose blood is sterilized for a period of time but who nevertheless eventually succumb (3) those patients with apparent cure

The best results with sulfapyridine alone or when combined with heparin are obtained in those patients with a mild infection in which the diagnosis often is not absolute and in which the drug clears the blood stream of organisms and lowers the fever Drug resistance may develop with *Streptococcus viridans* against one drug but not necessarily against all of them

During an epidemic of cerebrospinal fever in the Dinka districts of the Anglo-Egyptian Sudan Bryant and Fairman[15] encountered 22 cases of *tetanus* By administering 1 0 to 1 5 gm (gr 15 to 22) doses of sulfapyridine intravenously or intramuscularly with continuous or intermittent narcosis with sodium evipan 17 cases recovered These authors favor serum administration but state that if serum is unobtainable sulfapyridine with narcosis may be very useful

TABLE VII

INFECTIONS IN WHICH SULFAPYRIDINE IS INEFFECTIVE

Anaerobic streptococcal infection	Syphilis
Anaerobic infection (Clostridia)	Tuberculosis
Cl oedematiens	Tularemia
Cl Welchii	Typhoid fever
Blastomycosis	Virus infections
Diphtheria	Common cold
Paratyphoid fever	Encephalitis
Psittacosis	Herpes
Sinusitis chronic	Influenza
Skin infection	Rabies
Impetigo	Yaws
Pustular dermatitis	
Sycosis	

In the treatment of gas gangrene sulfapyridine may be effective when combined with serum or antitoxin This is discussed subsequently under local therapy with these drugs In psittacosis recovery may occur[19] and in tularemia the disease may advance[156] in spite of sulfapyridine therapy As with sulfanilamide sulfapyridine in vitro may have a bacteriostatic effect on the tubercle bacillus but it requires concentrations much higher than are attainable clinically Tuberculosis in the human has not responded to sulfapyridine

Other Medication Along with Sulfapyridine

As with sulfanilamide most other drugs may be administered in conjunction with sulfapyridine if they are indicated It has been found experimentally that the effects of codeine on rats mice and rabbits and of morphine on mice are enhanced by sulfapyridine[illegible] The increased activity of the drugs after sulfapyridine was evident not only in the prolongation of their action but also in the intensity of their effects and in the increase of their toxicity This has not been substantiated in the human patient Experimentally also sulfapyridine has been found to increase the effects of certain barbiturates but clinical evidence to the contrary has been presented by Smith[illegible] He treated many patients with gas gangrene and other infections having high blood levels of sulfapyridine with large doses of pentothal sodium and noticed no untoward effects whatsoever In fact he believed the nausea and vomiting from sulfapyridine to be lessened by the narcosis

Toxic Effects of Sulfapyridine

The toxic effects of sulfapyridine are essentially similar to those of sulfanilamide with particular emphasis on some and less on others Anorexia nausea and vomiting are particularly prominent manifestations of this drug and it along with sulfathiazole has frequent renal toxic effects Cyanosis acidosis hepatitis and certain blood toxic effects are uncommon as compared with sulfanilamide On the other hand rash and drug fever are quite common with sulfapyridine

Originally sulfapyridine was thought to be considerably less toxic than sulfanilamide but subsequently it became evident that the false impression was due to sulfapyridine when given orally having a lesser absorption from the intestines By the use of the sodium salt of sulfapyridine it has been shown that either on the basis of amount absorbed or of blood concentration sulfapyridine is about twice as toxic acutely as is sulfanilamide On the basis of death of mice sulfapyridine is twice as toxic acutely as sulfanilamide but only half as toxic to the hematopoietic system a preferential affect Acetyl sulfapyridine is also more toxic than acetylsulfanilamide

With this drug there is also a relationship in certain instances between large doses and high blood level and the toxic effects The large doses are more likely to affect the kidneys Occasional instances are recorded[illegible] however where as much as a total of 6 952 gr (463 5 gm) of sulfapyridine was given over a period of 10 weeks with no ill effects whatsoever

Sulfapyridine like sulfanilamide causes also an increase in urinary porphyrin excretion which may be a factor in toxicity With sulfanilamide the higher the blood level the more porphyrin is excreted and the more toxic become the manifestations This is not the case with sulfapyridine for higher blood levels do not cause more porphyrin excretion Thus from a standpoint of porphyrinuria sulfapyridine is no more toxic than sulfanilamide[23]

Anorexia nausea and *vomiting* of serious degree is a problem peculiar to sulfapyridine In a review of 3 500 cases in which this drug had been used[24] these symptoms were found to occur in 36 per cent severely in 12 per cent In numerous smaller series the percentage has been even higher up to 60 per cent These symptoms apparently are neither of gastrointestinal nor central nervous origin exclusively and proof of this has been obtained[25] by finding that vomiting movements occurred in gastrectomized and partially eviscerated animals within 15 to 20 minutes after the intravenous injection of the drug Both the controls and the animals operated upon were affected at the same blood level 25 to 30 mgm per cent In addition dogs did not vomit when a solution of sulfapyridine was applied directly to the emetic center in the floor of the fourth ventricle The evidence suggests that the vomiting is mediated through a reflex stimulation of the vomiting center certainly not exclusively from the gastrointestinal tract but probably from some other site or sites In a further effect upon the gastrointestinal tract unexplained bleeding has occurred in a few instances death resulting in one patient

The *renal toxic effects* of sulfapyridine and sulfathiazole are unusually interesting and may be very serious leading to anuria azotemia and even death The pathological physiology of this complication has been discussed under the pharmacology of these drugs In Klumpp s series[24] renal symptoms occurred in 6 per cent of cases This is less than with sulfathiazole The manifestations are both chemical and mechanical due to the precipitation of acetyl sulfapyridine crystals in the urine and their lodgement in the renal tubules or pelves ureters and bladder These substances probably have an effect on the renal parenchyma also An acute hemorrhagic nephritis has been reported The first sign usually is microscopic then macroscopic hematuria although neither may occur There may be severe pain of renal colic Oliguria followed by anuria is a bad omen and generally signifies mechanical block due to crystals in the urinary tract Concretions may result These are not visualized by x ray but calcium can become deposited about these concretions which act as nucleus and thus the shell may become radio opaque Nitrogen retention occurs frequently and has been reported as high as

150 to 175 mgm per cent of blood urea nitrogen One point of interest which may be culled from the cases cited in several publications is that patients who developed hematuria at the time of the first sulfapyridine administration at a later period when the drug was given a second time have developed hematuria again The same may be said of anuria in spite of forcing of fluids

Anemia either of the acute or chronic type is uncommon after sulfapyridine but may occur When the drug is continued long enough frequently there is a moderate drop in hemoglobin concentration but seldom much change in red blood cell level When anemia does occur the features are essentially those already described under sulfanilamide A few cases of *thrombocytopenic purpura* have been reported during sulfapyridine therapy

It has been stated that a reduction of the leukocytes is encountered not infrequently in children receiving sulfapyridine and the development of *agranulocytosis* either in children or in adults is perhaps even more frequent than with sulfanilamide As with that drug many cases are reported after receiving small doses over a long period of time That nutrition and possibly race may be factors is suggested by the report of van Heukelom[76] in which 30 of 233 cases of various infections in poorly nourished Javanese and Chinese treated with sulfapyridine developed agranulocytosis Only two of them died *Hyperleukocytosis* may occur with acute hemolytic anemia

Drug fever occurring with sulfapyridine in about 5 per cent of cases is very similar to that described under sulfanilamide

Skin rashes due to this drug are not as frequent as with sulfanilamide or sulfathiazole They are very similar to those discussed under sulfanilamide Acquired sensitivity more common with sulfathiazole has been reported also with sulfapyridine Several interesting lesions of the mucous membranes have been described following therapy with sulfapyridine Mayo and Finlayson[77] describe the case of a woman of 47 who was treated with sulfapyridine for bronchopneumonia and who developed cracked lips dysphagia inflamed conjunctivæ and vaginæ and vulval exudate which on separating left raw bleeding surfaces In a boy of 5 years treated for pneumococcal meningitis for 15 days with sulfapyridine (1 740 gr) there developed a skin rash and coincidently there appeared on the lips buccal mucous membranes gums and pharyngeal mucosa[78] a heavy bluish white gelatinous membrane

There have been a few isolated reports of *hepatitis* following sulfapyridine but it is rare in comparison to sulfanilamide Brown and his associates[79] have employed sulfapyridine successfully on three occasions

to control pneumonia in patients who also had severe hepatitis without observing that the liver dysfunction was increased It should be re marked parenthetically that when sulfapyridine is used in treating patients with pneumonia the occurrence of jaundice cannot be attributed always to the drug because the incidence of jaundice in pneumonia is approximately 7 per cent

Cerebral toxic effects are rather frequent with sulfapyridine dizziness occurring in about 9 per cent of cases and a syndrome suggesting a mild attack of encephalitis appearing occasionally Johnstone and Lorgaes[30] have encountered 5 instances in a series of 70 cases of menin gococcal meningitis in which large doses of sulfapyridine gave rise to cerebral symptoms simulating closely those of acute meningitis This syndrome was characterized by irritability restlessness confusion and stupor with signs of meningitis in the face of subsiding fever and a clearing spinal fluid Actually therefore this was a meningismus and it had no relation to the blood level of the drug It is easy to see how such manifestations could be ascribed to the infection yet when the drug was stopped the symptoms subsided promptly

The *treatment of the toxic manifestations* of sulfapyridine on the whole is similar to that described under sulfanilamide namely withdrawal of the drug forcing fluids using oxygen or methylene blue for methemoglobinemia and cyanosis and giving transfusion for anemia

For the nausea and vomiting many measures have been tried and none are uniformly successful except to stop the drug Administering the drug in a vehicle such as milk jellies admulcent gel (a proprietary preparation) ½ strength of mucilage of tragacanth and similar methods may lessen gastric irritation The use of sedatives such as phenobarbital 30 to 60 mgm (½ to 1 gr) orally or subcutaneously one half hour before the drug administration has been found useful If the vomiting becomes intractable and it is necessary to administer this particular drug the intravenous route may be resorted to Otherwise one of the other sulfonamide compounds may be substituted

For the renal complications of sulfapyridine the treatment will depend upon the severity of the manifestations It is not necessary to stop the drug for microscopic hematuria but caution and strict observation is necessary in continuing therapy At this stage the forcing of fluids to a daily output of urine of 1 500 c c is advisable With the appearance of an appreciable number of acetylsulfapyridine crystals in the urine it has been advised that the administration of sodium bicarbonate to pro duce an alkaline urine for the solution of the crystals might be helpful Further observation has not substantiated this idea

With macroscopic hematuria renal colic or anuria the drug is to be stopped In these more severe manifestations it has seemed helpful to insure by increased fluid intake a 24 hourly urine output of 1 000 to 1 500 c.c and with oliguria to administer by continuous intravenous drip 300 to 400 c c of 20 to 25 per cent dextrose solution in two to four hours For anuria the above treatment may have to be supplemented with cystoscopy the catheterization of one or both ureters and frequent lavaging of the ureter and renal pelvis with warm distilled water In this connection it may be added that with sulfapyridine crystals such retrograde kidney washes have seemed to be more effective than with sulfathiazole

Hypnotics such as nembutal in subhypnotic doses have been suggested to be given along with sulfapyridine in patients who experience central nervous system side effects from this drug Should a summation effect occur as has been reported in animal picrotoxin may be used as the antidote

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PART IV

Sulfathiazole

Sulfathiazole another analogue of sulfanilamide has replaced both sulfanilamide and sulfapyridine in the treatment of numerous infections This is to be attributed to its rapid absorption and hence quick action its equal effectiveness in many of the diseases and particularly the lessened number and severity of its toxic manifestations In addition it has proved to be much more effective against staphylococcal infection than either of the other two drugs Although considered to be less toxic than the other two drugs as a general statement of fact certain of its side effects may be more severe and more frequent

Methods of Administration and Dosage of Sulfathiazole

The methods of administration and dosage are very similar to those discussed under sulfapyridine Sulfathiazole *by mouth* is the method of choice because of its ease of absorption and minimum of nausea and vomiting when compared with sulfapyridine It is supplied in tablets of 0 25 and 0 5 gm (3¾ and 7½ gr) for oral use These need not be taken with a vehicle In patients severely ill with an infection amenable to this drug it has become common practice to administer an initial dose of 3 0 to 4 0 gm (gr 45 to 60) followed by 1 0 to 1 5 gm (gr 15 to 22) every 3 to 4 hours The blood levels with this dosage will average 4 to 10 mgm per cent Sulfathiazole seems to be tolerated best with food in the stomach and it has been found beneficial to use dilute hydrochloric acid rather than alkalies along with it

For *subcutaneous administration* sulfathiazole solution may be prepared much the same as discussed under sulfanilamide Such a solution may be prepared by adding 5 0 gm of the powdered drug to a liter of 5 per cent glucose in distilled water at a temperature between 90° and 100° C Boiling is to be avoided after adding the sulfathiazole With subcutaneous administration the maximum levels of sulfathiazole are reached more promptly than with sulfanilamide with sulfanilamide however the maximum blood levels are higher than with sulfathiazole This method used particularly when the patient cannot swallow or is moribund supplies also fluid and nourishment Sodium sulfathiazole may be given orally using an initial dose of 4 0 to 5 0 gm (gr 60 to 75) followed

by 1 0 gm (gr 15) every four hours This method gives higher blood levels than sulfathiazole by mouth

The sodium salt of sulfathiazole is to be used for *intravenous administration* It is to be prepared similarly to the sodium salt of sulfapyridine One gram (15 gr) of sodium sulfathiazole is dissolved readily in 100 c c of distilled water This must be given slowly By this route of administration higher blood levels are attainable The dosage is as outlined under sodium sulfapyridine It is only about one half as toxic as the latter drug

Sulfathiazole may be administered *rectally* but fortunately the oral administration of sulfathiazole is so satisfactory and causes nausea and vomiting of significant degree so infrequently that the rectal route is rarely if ever indicated If it is desired to use this method it is advisable to give a soap and water enema a few hours before using the drug Sulfathiazole may be given 5 0 gm suspended in 300 c c tap water Sodium sulfathiazole is rather irritating and its absorption by rectum is slow and quite incomplete It is not to be used by this route

The local administration of sulfathiazole is discussed under the local application of these drugs (see Part VIII)

The Clinical Uses of Sulfathiazole

Sulfathiazole was accepted quickly after its introduction and in the two years that have followed it has proved itself to be of distinct value in numerous infections superseding both sulfanilamide and sulfapyridine in many instances For several reasons which are discussed in the respective infections it has proved to be superior in pneumococcal pneumonia gonococcal infections particularly urethritis in the male and staphylococcal infections Apparently not always as effective as sulfanilamide and sulfapyridine it has replaced them in usage frequently because of its lesser immediate toxic effects However in some respects it is more toxic making its withdrawal at times necessary The particular advantages that sulfathiazole has over these other two drugs especially over sulfapyridine include a more uniform absorption less conjugation after absorption less tendency to cause serious nausea or to provoke vomiting and a greater effectiveness against the staphylococcus

In Table VIII are listed infections in which sulfathiazole has been used with distinctly beneficial results It has become the drug of choice in those diseases italicized

In the reports of the Council on Pharmacy and Chemistry of the American Medical Association the clinical use of sulfathiazole has been

TABLE VIII

INFECTIONS IN WHICH SULFATHIAZOLE IS EFFECTIVE*

Bacillus coli tissue infections	*Pneumonia*
Gonococcal infections	*Septicemia*
Arthriti	Skin infections
Male gonorrhea	Beta hemolytic streptococcal infections
Pneumococcal infections	Urinary tract infections
Bacteremia	Aerobacter aerogenes
Pneumonia	Bacillu pyocyaneu
Staphylococcal infections	Escherichia coli
Arthritis	Staphylococcus *albus*
Carbuncles	Staphylococcus *aureus*
Cellulitis	
Osteomyelitis	

* Word in italics are those condition in which sulfathiazole i especially effective

given as for pneumococcal pneumonia staphylococcus aureus B coli infections and gonorrhea in the male

The greatest usefulness of sulfathiazole has been found in the treatment of pneumococcal pneumonia gonococcal and staphylococcal infections These will be considered in turn

In *pneumococcal infections* particularly bacteremia and pneumonia it has come to supplant sulfapyridine not that it is any more effective in lowering the mortality rate as subsequent data will demonstrate but because it gives rise to much less nausea and vomiting Comparatively speaking it may be stated that in large series of cases of pneumococcal pneumonia sulfapyridine causes nausea and vomiting in about 60 per cent of cases sulfathiazole in approximately 20 per cent This has a distinct advantage in the continuation of treatment and facilitates use by the oral route Further it is absorbed rapidly and completely from the gastrointestinal tract and after its absorption has a high antipneumococcal potency It is conjugated less than sulfapyridine

Because of its rapid excretion frequently it is somewhat more difficult to maintain an adequate blood level with it For that reason it has been found advisable to give somewhat larger doses of sulfathiazole than of sulfapyridine namely administering an initial dose of 4 0 gm (gr 60) then giving 1 0 to 1 5 gm (gr 15 to 22) every four hours until the temperature has been near normal for 48 hours As brought out in the discussion of sulfapyridine the temperature may not drop as rapidly with sulfathiazole If at the end of 48 hours the temperature has not dropped below 101° F rectally and if the blood level of sulfathiazole is under 4 mgm per cent it may be necessary to supplement treatment

with intravenous sodium sulfathiazole 0 06 gm per kilo as for sulfapyridine Oral administration is to be continued in the same amounts as before A blood level of 4 0 to 8 0 mgm per cent is satisfactory in almost all cases As a matter of fact under ordinary dosage as just outlined the blood level will not exceed 8 0 mgm per cent unless there is an associated renal insufficiency In other words when the blood level exceeds 8 mgm per cent and the dosage has been usual suspect renal insufficiency

Sulfathiazole clears rapidly the blood stream of organisms and as with sulfapyridine it remains clear unless a complication is present In terms of antibody response sulfathiazole is thought to stimulate the immune mechanism of patients more than sulfapyridine which is interpreted to mean that sulfapyridine is a somewhat more powerful antipneumococcal agent than sulfathiazole[31] However this difference does not appear to be too significant for at the end of 72 hours the effect of the two drugs on the temperature is practically the same Also the length of hospitalization and the incidence of complications are practically identical

In a compilation of 1 400 cases of pneumococcal pneumonia collected by the writer the mortality rate varied from zero per cent in small groups of cases to as high as 12 per cent with an average of 7 6 per cent Although the drug has not been used as long and not nearly as many cases have been reported at the time of this writing the same general trend seems evident as discussed under sulfapyridine namely a tendency to a higher mortality rate in hospital statistics

With sulfathiazole too serum in addition has not lowered appreciably the mortality serum is indicated as supplemental therapy under the same conditions as discussed for sulfapyridine As a crude estimate from reported series it may be stated that serum in addition to sulfathiazole or sulfapyridine is indicated in about 10 per cent of cases of pneumococcal pneumonia

For infants and children the total daily dose is 1 gr per pound of body weight One fourth to one half of this amount may be given as an initial dose then one eighth of the total dose may be given every 3 hours until the temperature has been normal for 48 hours Collected cases which number only slightly over 300 show a mortality much lower in children 2 to 3 per cent In fact one series of 77 cases[32] had no mortality These authors feel that in children the blood level of the drug seems to be no guide to therapeutic effectiveness and that blood levels need to be studied only in cases where the drug is ineffective In the treatment of pneumococcal pneumonia with sulfathiazole the same factors in prognosis obtain as with sulfapyridine

In connection with pneumonia a few remarks should be made concerning *virus pneumonia* Sulfathiazole as well as the other sulfonamide drugs is ineffective in virus pneumonia and is not to be used At the meeting of the Association of American Physicians (1941) Finland presented evidence to show that to withhold sulfathiazole or perhaps the newer drug sulfadiazine may be unwarranted for he found a rather high incidence of staphylococcal infection of the lung symbiotic with influenzal pneumonia against which sulfathiazole is very effective Upon this evidence it is suggested that where a diagnosis of virus pneumonia has been made sulfathiazole be given for several days both as treatment and to prevent a complicating staphylococcal pneumonia The significance of this finding lies in the fact that the combined infection carries a very high mortality rate

That sulfathiazole penetrates poorly into the cerebrospinal fluid has been discussed but whether this likewise is true in patients with meningitis has not been established definitely Cerebrospinal fluid concentrations of sulfathiazole which occur during treatment of meningitis generally do not exceed 25 per cent of the plasma concentrations this is explained probably by the binding of the drug to the plasma proteins (albumin) of the blood (Davis) Whether the drug is efficacious in the treatment of *pneumococcal meningitis* has not been settled but some investigators think not

Until more is known of the efficacy of this drug and its newer preparations it is well to call attention to Finland s effective therapy of pneumococcal meningitis[33] namely the administration of type specific antiserum intravenously followed later by bleeding the patient letting the blood clot to separate the serum and then injecting this serum back into the patient s spinal canal

Most outstanding results have been achieved in the treatment of *gonococcal infections* with sulfathiazol particularly *gonorrheal urethritis* in the male Its advantages over sulfanilamide and sulfapyridine are several First the actual rate of cure is higher With sulfanilamide the percentages of cure have ranged from 10 to 70 per cent averaging about 60 depending upon the stage of the disease and the conditions under which treatment was carried out with sulfapyridine the results are better averaging about 75 per cent with sulfathiazole the lowest percentage of cure recorded is 81 with several reports of 100 per cent In a total of 2 350 cases compiled by the writer the average rate of cure was 94 99 per cent Second such results seem to obtain whether the disease is acute or chronic (sulfanilamide is not so effective in acute first infections) and whether the patient was treated in the hospital or as an ambulatory

patient Third the time of disappearance of discharge and the interval necessary to obtain cure are shorter with sulfathiazole than with the other two drugs Fourth resistant strains after treatment and carrier states are less common with this drug Resistant strains of gonococcus do occur however both natural and acquired and treatment should be directed accordingly as discussed further on Fifth the immediate toxic effects of the drug are less Finally sulfathiazole frequently is effective when either sulfanilamide or sulfapyridine or both have failed to clear up the infection

Various plans of dosage have been outlined for the treatment of gonorrhea with sulfathiazole A satisfactory method is to use 3 0 to 4 0 gm (gr 45 to 60) by mouth the first day then 2 0 gm (gr 30) a day for 9 days The advantage of a large initial dose is the probability of avoiding the acquisition of a resistant strain of gonococcus With this routine the discharge ceases usually in 3 to 5 days and cultures become negative after 10 days If symptoms or a discharge remain after 10 days of such treatment it is probable that a drug resistant strain of the organism is present or a complication has arisen although complications such as epididymitis prostatitis prostatovesiculitis and cowperitis usually respond favorably Under such circumstances probably it is advisable to change to sulfapyridine sulfadiazine or possibly sulfacetimide

It has become an outstanding fact in the treatment of urogenital gonorrhea particularly with sulfathiazole that a high blood level of concentration is not necessary Blood levels of 1 5 to 3 0 mgm per cent frequently are effective

Some investigators have continued local irrigations in addition to the sulfonamide both to encourage further attendance for treatment and for the benefit of any who may not be helped by these drugs Pelouze even has recommended in an efficient office practice the omission of sulfonamides in treating acute anterior urethritis where there is no immediate danger of posterior involvement since local treatment usually brings about a prompt cure

Even with the most remarkable successes there still remains an irreducible minimum of failures estimated variously from 5 to 12 per cent For these cases artificial fever therapy in addition to the sulfonamide has been found to aid in the cure of the patient A satisfactory method seems to be the administration of sulfathiazole for 18 to 24 hours followed by a fever session of 8 hours with temperatures of 105°–106° F

In women acute gonorrheal infections respond equally as well as those of the male but chronic pelvic inflammatory disease often needs other measures in addition Females may require somewhat larger doses as

3.0 to 4.0 gm. (gr. 45 to 60) for 4 or 5 days, then 2.0 gm. a day, not infrequently the treatment must be continued longer than in men. Other secondary vaginal organisms frequently disappear also with this treatment. Interestingly trichimonas infection of the vagina has occurred in about 15 per cent of a large group of clinic cases and there seems to have been an increase of this infection in females who are being treated with sulfathiazole for acute gonorrhea. Other treatment in addition to the sulfonamide such as rest, local heat, potassium permanganate and lactic acid is used by some observers as a further step in the prevention of infectiousness during drug therapy.

Sulfathiazole has been found to be quite effective in the treatment of *vulvovaginitis* and *gonorrheal ophthalmia* in infants and children. The dose of 0.75 to 1.0 gm. (gr. 12 to 15) per 20 pounds body weight a day, divided into four equal amounts, is tolerated well. Sulfathiazole has been found effective for vulvovaginitis when used on this basis, treatment being carried out for two weeks the first month, then one week for each of the next two months.

In the treatment of gonorrhea attention should be called to two complications rather peculiar to sulfathiazole that may result from the medication and not from the disease. These are a *toxic conjunctivitis* and a *toxic arthritis*. A peculiar conjunctivitis that has been seen only after sulfathiazole can confuse the issue in gonorrheal treatment, making one suspect gonorrheal ophthalmia. It usually subsides promptly upon withdrawal of the drug. Some patients receiving this drug, occasionally those receiving sulfanilamide, develop acute, tender, swollen joints which should not be confused with gonococcal arthritis when the drug is being used to treat gonorrhea. The symptom subsides upon stopping the drug and forcing fluids.

Of the three drugs, sulfanilamide, sulfapyridine and sulfathiazole, the last has proved to be of most benefit in *staphylococcal infections*. What results are to be obtained with some of the newer compounds will be awaited with interest, but sulfathiazole has proved to be quite effective in clearing the blood stream of this organism. In vitro some bactericidal as well as bacteriostatic effect has been demonstrated and the same probably holds true in vivo. Doses of 6.0 and even 8.0 gm. (90 to 120 gr.) a day may be necessary to clear the blood stream of organisms, and because metastatic foci and abscesses frequently continue to pour organisms into the blood stream, these should be sought for and drained. A high blood level, 10 to 15 mgm. per cent, may become necessary to overcome the infection. In a total of 50 collected cases of staphylococcal septicemia 38.75 per cent recovered under sulfathiazole therapy. In

the case of a girl of 12 with chills fever heart murmurs splenomegaly and positive blood cultures diagnosed originally as subacute bacterial endocarditis the organism was identified subsequently as staphylococcus aureus with an osteomyelitis of the left femur The colony counts were over 100 per c c of blood a blood concentration of 12 mgm per cent of sulfathiazole cleared the blood stream of organisms in 4 days Proper surgical attack on the osteomyelitis resulted in complete clinical cure

In many other types of staphylococcal infections such as furuncle carbuncle cellulitis cortical abscess of the kidney sinusitis otitis media mastoiditis epidural abscess meningitis and staphylococcal pneumonia this drug has proved very beneficial Levels of blood concentration of 6 to 8 mgm per cent usually are sufficient Because of the inhibiting effect of peptone and like substances on sulfathiazole it is best when feasible to drain mechanically any collections of pus in these conditions Experience has shown that the possible toxic reactions to this drug are such that it seems best not to use it in the treatment of minor staphylococcal infections such as localized boils and mild furunculosis For carbuncle the initial dose for adults should be 4 0 gm (gr 60) followed by 1 gm (gr 15) every four hours day and night for 5 to 7 days In diffuse staphylococcal cellulitis lymphangitis or acute osteomyelitis 4 0 gm (gr 60) should be given as an initial dose followed by 1 5 gm (gr 22) 4 hourly as long as evidence of spreading infection continues The dose then may be reduced to 1 0 gm (gr 15) every four hours

Mention should be made of a recent suggestion by Osgood Joski and Brownlee[234] of combining neoarsphenamine and sulfathiazole in the treatment of severe staphylococcal infections In bone marrow studies they found that the two drugs used simultaneously against staphylococci inoculated into the bone marrow produced better results than either chemical alone Sulfathiazole is given by mouth to insure a blood level of 8 to 10 mgm per cent and neoarsphenamine because of its rapid disappearance from the blood stream is given by multiple injections during the day The total daily dose of neoarsphenamine is calculated by the formula $\frac{\text{body weight in pounds}}{330}$ = grams of neoarsphenamine to be given in four divided doses After the first day the daily dose is three fourths this amount until the patient has been afebrile for 6 to 10 days No adequate clinical data are available concerning the virtues of this method

In certain of these conditions such as skin infections osteomyelitis and brain abscess the local application of sulfathiazole is considered later in this chapter under the local use of sulfonamides in Part VIII

Sulfathiazole has proved its worth also in the treatment of *urinary tract infections* Because of the numerous organisms that may cause infection in this system as each new compound is introduced for clinical use series of tests and observations with each organism become necessary in order to learn again when to use which drug where Such observations with sulfathiazole have been carried out by Helmholtz[35] with the finding that this drug is effective against most bacterial invaders of the urinary tract but its particular usefulness is against infections due to *staphylococci* and *Streptococcus fecalis* Both the pH of the urine and the blood concentration with its resulting urine concentration of the drug are variants in its action In a low blood concentration with urine pH in the vicinity of 7 5 sulfathiazole is very effective against *staphylococci* even appreciably bactericidal So far sulfathiazole has proved to be the most effective of the sulfonamides against *Streptococcus fecalis* so often remaining after mixed infections have been eradicated by either sulfanilamide or sulfapyridine and so resistant to treatment Here a high blood concentration with the urine toward a pH of 5 5 to 6 0 produces the best results A moderate blood level with urine pH of 6 5 to 7 5 produces highly satisfactory results with *B coli* and *Proteus ammoniæ* but a high blood and urine level with the urine alkaline may be necessary for the eradication of *Aerobacter aerogenes* *Pseudomonas aeruginosa* is relatively resistant to sulfathiazole action as with sulfanilamide and sulfapyridine

The ease with which sulfathiazole is excreted from the body through the kidneys makes the attainment of high urinary levels easier than with sulfanilamide and sulfapyridine hence the observation that frequently very satisfactory response of urinary tract infection can be obtained on only small doses of sulfathiazole Thus as low a concentration in the urine as 10 mgm per cent will give striking results in many urinary tract infections except possibly with *Streptococcus fecalis* and *Pseudomonas aeruginosa* It appears from clinical studies and studies in vitro[236] that a urine concentration of between 50 and 200 mgm of free drug per 100 c c urine is sufficient to sterilize the urine in most instances To obtain this effect an initial dose of 2 gm (gr 30) followed by 1 0 gm (gr 15) every four hours and after several days 1 0 gm every six hours will produce such concentrations It is stated this way because most studies in this connection are carried out in terms of urine concentration rather than blood concentration However the above method will give an average blood level of 4 mgm per cent In this procedure the restriction of fluid is not necessary

In mixed infections of the urinary tract sulfathiazole has seemed more

effective also than sulfanilamide and just as effective as sulfapyridine In a series of 400 cases where mixed infections were present sulfanilamide produced good results in 20 per cent sulfapyridine and sulfathiazole in 50 per cent (Alyea)

As cited previously due to the ease and rapidity of excretion this drug may be extremely useful in instances with nitrogen retention where minimal doses only seem safe and where small doses may cure the infection[74]

Mention should be made of the effect of sulfathiazole on *beta hemolytic streptococci* It has been found to be an effective chemotherapeutic agent against strains A D and C of Lancefield both in vitro and in vivo Because of the lesser incidence of cyanosis nausea and vomiting when compared to sulfanilamide sulfathiazole has been used extensively in these infections with gratifying results At the present time however sulfadiazine promises to become the drug of choice in the treatment of infections due to this organism

Sulfathiazole has not been tried in the vast variety of infectious conditions to which sulfanilamide and sulfapyridine have been applied Yet in a number of them good results have been obtained in a few instances and in others the evidence is somewhat conflicting These have been listed in Table IX together as infections in which the effect of sulfathiazole is doubtful

TABLE IX

INFECTIONS IN WHICH SULFATHIAZOLE EFFECT IS DOUBTFUL

Aphthous stomatitis	Plague
Bacillary dysentery	Shigella infection
Brucella infections	Sinusitis chronic
Lymphogranuloma venereum	Streptococcus viridans subacute bacterial endocarditis
Malaria	Tularemia
Meningococcus infection Meningitis	Typhoid fever
Paratyphoid fever	Ulcerative colitis

Recurrent scarring painful *aphthæ of the tongue and mouth* of unknown etiology have been reported to respond to 4 0 to 6 0 gm a day of sulfathiazole[37] Certain forms of *bacillary dysentery* and *Shigella infections* have been reported to respond in a few instances to either sulfapyridine or sulfathiazole As a matter of fact the reports concerning sulfathiazole in the treatment of bacillary dysentery particularly in children have been quite impressive In six reported series coming chiefly from the

South the best results were obtained in those patients whose stool cultures were positive for *S paradysenteriæ* In patients with positive stool cultures sulfathiazole decreased the duration of illness and decreased the mortality Stool cultures were made negative by this treatment[38] The plan of treatment has been a 24 hour dose of 1½ to 2 gr per pound body weight half of which is given as an initial dose then one sixth the total dose every four hours throughout the 24 hours until the temperature and the stools have returned to normal Supportive measures are indicated in addition As more evidence is accumulated it is probable that sulfaguanidine will become the drug of choice for this disease

In *lymphogranuloma venereum* sulfathiazole has seemed somewhat better than sulfanilamide particularly if rectal stricture is not present It seems very effective in the inguinal cases although the number of reported instances is not large Small doses such as 1 5 gm (22 gr) three times a day for three weeks and then 1 0 gm (gr 15) thrice daily for another three weeks has given satisfactory results

In naturally occurring *malaria* sulfathiazole is thought to decrease the number of organisms in the blood stream but in therapeutically induced malaria it has had little or no effect Very little evidence has been presented regarding the treatment of *meningococcus meningitis* with this drug except Banks s statement[39] that sulfathiazole in spite of theoretical shortcomings is highly effective

In certain *infections involving the upper respiratory tract sinuses mastoids and adjacent structures* encouraging results have been obtained with this drug Turnbull[40] reported very good results with sodium sulfathiazole used locally in the sinuses but his results have been not only unconfirmed but criticized inasmuch as the salt is too irritating to the mucosa In chronic *otitis media* the results are not as good as in the acute stage Along with heparin sulfathiazole has seemed to be helpful in recovery of isolated instances of *staphylococcal cavernous sinus thrombosis*

The subject of *streptococcus viridans bacterial endocarditis* is discussed more fully under sulfanilamide and sulfapyridine Sulfathiazole has not seemed to be any more helpful if as good particularly not as good as sulfapyridine One reason perhaps is the frequent difficulty of maintaining an adequate blood level of sulfathiazole The drug will eradicate this organism from the blood stream in septicemia without heart valve involvement[41]

As discussed under staphylococcal infections Osgood and his associates have produced laboratory evidence to suggest[116] that neoarsphenamine in

persisting blood concentrations of 1 150 000 along with one of the sulfonamides preferably sulfathiazole provides an effective chemotherapeutic attack against most strains of *Streptococcus viridans* and may prove useful in the treatment of subacute bacterial endocarditis in the human patient. To maintain a blood concentration of 1 150 000 of neoarsphenamine the formula applies as given already under staphylococcal infections. The blood concentration of sulfathiazole should be 8 to 10 mgm per cent. No clinical reports of this method are available.

In vitro sulfathiazole has shown itself to be superior to sulfanilamide, sulfapyridine and sulfamethylthiazole against the colon typhoid dysentery groups of organisms and several isolated instances of helpful effect have been reported in typhoid fever in the human patient. When used in large doses it was concluded that at least it had no harmful effects in this disease.

Infections in which Sulfathiazole is Ineffective

Although there has been no satisfactory accumulation of data concerning unsatisfactory use of this drug in many diseases except in virus infections, several lists have appeared in the literature enumerating the same diseases listed in Tables IV and VII under sulfanilamide and sulfapyridine.

Other Drug Medication along with Sulfathiazole

Other treatment including drug medication may be given along with sulfathiazole but not combined with it as discussed under this heading for sulfanilamide and sulfapyridine. Phenobarbital combined with sulfathiazole has led to severe toxic reactions and death.

Toxic Effects of Sulfathiazole

In some respects sulfathiazole is considered to be less toxic than sulfanilamide or sulfapyridine. That is true for certain of its manifestations but for others it is definitely more toxic. In acute toxicity experiments in animals as measured by the parenteral injection of sodium salts of these compounds sulfathiazole is approximately 1/3 more toxic than sulfanilamide and ½ to 1/3 as toxic as sulfapyridine. In chronic toxicity experiments the drug is definitely more poisonous, producing in mice microscopic lesions of the kidneys, livers and spleen.

In the human patient about 15 per cent of individuals receiving

sulfathiazole complain of various toxic symptoms of which fever and certain skin manifestations are more common than with either of the other two drugs In addition there are several manifestations from sulfathiazole that are peculiar to it

Cyanosis lowering of CO_2 combining power of blood plasma and toxic effects on the bone marrow or peripheral blood cells are distinctly uncommon after sulfathiazole Isolated instances of acute hemolytic anemia and agranulocytosis have been reported and mention has been made of the frequency of eosinophilia following this drug

Nausea and vomiting does occur particularly with high blood levels of the drug but they are only about one third as frequent as with sulfapyridine The parenteral administration likewise can cause these same symptoms

Fever occurring in about the same incidence as with sulfanilamide and more often than with sulfapyridine has essentially the same characteristics with this drug as discussed under sulfanilamide As with the other drugs experience indicates that unless it can be proved otherwise the sudden recurrence of fever after a few days of essentially normal temperature should be regarded tentatively as toxic fever and chemotherapy should be stopped

Various *skin eruptions* occur somewhat more frequently after sulfathiazole therapy than after the other drugs The types of rash fall chiefly into three groups maculopapular urticarial and one more or less distinctive of this drug which is very similar to an erythema nodosum In the last one lesions exactly similar to erythema nodosum appear as reddened elevations on the anterior surfaces of the legs sometimes on the arms They are painful and tender to touch and may have an associated leukocytosis They may persist for several days after the drug is stopped

In the treatment of bacteremia with this drug either streptococcal or staphylococcal the writer has been confronted several times with the appearance of severe and peculiarly distributed *purpura hemorrhagica* with the problem whether one is dealing with a toxic rash or whether with petechial manifestations of the disease By careful puncture and culture of a lesion in two instances the invading organism was recovered proving that it was not due to the drug and the drug could be continued Ordinarily with the occurrence of a skin rash the drug is to be stopped and further administration is likely to cause a recurrence but it seems that may depend upon when the re administration is begun for there are several recorded instances in which the drug was stopped the rash disappeared and on reinstitution of sulfathiazole the patient tolerated the drug satisfactorily After a longer interval on the other hand and

particularly if previous skin reactions had occurred with one of the other sulfonamide compounds a toxic dermatological lesion may ensue

An *acquired sensitivity* to sulfathiazole has been shown to occur In studying a large group of cases from this standpoint Lyons and Balberor[24] found over 30 per cent of individuals unable to tolerate the drug if given at a later date The chief manifestation was a febrile reaction during the second course of sulfathiazole

Besides a nodular erythematous rash and acquired sensitivity a third manifestation rather peculiar to sulfathiazole is the development of *conjunctivitis* with injection of conjunctivae and scleræ It resembles in many respects pink eye and occurs generally between the fifth and ninth days Its appearance is heralded frequently by burning and smarting of the eyes and a watery discharge In some cases an element of heliosensitivity appears to exert an etiological role

Not distinctive of this drug but similar to sulfapyridine is the occurrence of calculi from the acetyl crystals in the *urinary tract* Because of the ease and rapidity with which this drug is excreted by the kidneys even though its percentage of conjugation is less this complication appears to occur more commonly than with sulfapyridine In the human patient hematuria oliguria anemia renal colic and nitrogen retention occur Elevation of blood pressure has been reported also On the other hand no symptoms may occur as in the case reported by Loewenberg[243] that of a woman of 49 treated for pneumonia with sulfathiazole in whom acetylsulfathiazole concretions were found in the kidneys ureters and bladder without any symptoms

As with sulfapyridine hematuria gross not microscopic is the indication to stop the drug The presence of crystals alone in the face of a normal urinary output is not to be considered an indication for the cessation of treatment If the fluid intake can be kept in the vicinity of 2 500 to 3 000 c c and the output at 1 500 c c a day and if the drug is discontinued immediately and intravenous fluids are administered with the first appearance of lumbar pain or bloody urine the danger from renal complications can be kept at a minimum Some investigators have felt that the simultaneous use of alkalies in amounts equal to the dose of the drug may decrease the incidence and quantity of urinary crystals in patients under treatment with sulfathiazole Compared to sulfapyridine it has been found that kidney and bladder washes are not as effective in eradicating sulfathiazole crystals from the urinary tract

Other toxic manifestations seen with either sulfanilamide or sulfapyridine are less common after sulfathiazole Mention has been made of *acute joint pain* which may be confusing during the treatment of gono

coccal infections but such manifestations as *hepatitis jaundice* and *central nervous system effects* such as dizziness psychosis and peripheral neuritis are rare

The *treatment of the toxic manifestations* of sulfathiazole consists of the same measures discussed under sulfanilamide and sulfapyridine namely withdrawal of the drug forcing of fluids and transfusion and oxygen if required For nausea and vomiting admulcent gel or some other vehicle may be helpful Whether to administer alkalies routinely for the possible prevention of urinary tract complications still is a moot question Their use probably will do no harm

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PART V

Sulfadiazine

Introduction

The fourth compound of the sulfonamide derivatives found to be acceptable for clinical use by the Council of Pharmacy and Chemistry is sulfadiazine There are numerous sulfadiazines chemically the name for certain heterocyclic derivatives of sulfanilamide that is derivatives which contain a closed ring system in which the atoms are of more than one kind One of these a pyrimidine analogue of sulfapyridine and sulfathiazole (2 sulfanilamidopyrimidine 2 sulfanilyl aminopyrimidine p amino N 2 pyrimidyl benzenesulfonamide) has been marketed as sulfadiazine instead of the more technically proper name sulfapyrimidine to avoid confusion with sulfapyridine Like the other two compounds of high potency it has the structure of sulfanilyl cyclic amidines 4 (NH)C H_4SO NHC N with the formula C H N_4O S The structural formula for sulfadiazine is given in the section on chemistry Further studies of the chemistry of this compound have shown it to be the least soluble approximately 1 0 mgm per 100 c c in water at 370 C as compared to 800 mgm for sulfanilamide 54 mgm for sulfapyridine 96 mgm for sulfathiazole and 220 mgm for sulfaguanidine Its solubility moreover varies with the temperature and the medium employed At 22 C it is soluble to 9 mgm per 100 c c in water 13 mgm per 100 c c in saline 136 mgm per 100 c c in blood and 06 mgm per 100 c c in serum At 37 C it is soluble to 19 mgm per 100 c c in saline 204 mgm per 100 c c in blood and 124 to 161 mgm per 100 c c in serum The solubility of sulfadiazine in 95 per cent alcohol at room temperature is 67 mgm per 100 c c Its optical properties demonstrate a cleavage pinacoidal at right angles perfect It is optically biaxial positive

As stated in the chapter on chemistry of the sulfonamides sulfadiazine is readily soluble in alkalies and mineral acids This has allowed for the preparation of the sodium salt for enteral and parenteral therapy which is receiving wide spread use *Sodium sulfadiazine* has a molecular weight of 73 and is very soluble in water (sulfadiazine 0 0123 sodium sulfadiazine 65 0 at 37 C) It has been accepted also by the Council of Pharmacy and Chemistry only for intravenous use and that preferably in a 5 per cent strength in solution The reaction of the 5 per cent and the 10 per cent solution is approximately the same pH 9 0–11 0 Sodium sulfadiazine is difficult to sterilize because it deteriorates on heat

ing, but its solution in sterilized distilled water is safe for injection because of its alkalinity and bactericidal action

When sulfadiazine first made its appearance, its cost was very high compared to the previous compounds due in part to the cost of new equipment and extensive research Now on a production basis in this country its cost continues to remain high due to expensive intermediate chemicals and a 6 step commercial process, two features which have prevented this drug from enjoying practically any use in England or the European continent during the present World War In fact it did not become available in England until May and June, 1942 Today the druggist is paying $0 75 to 0 80 for 100 tablets of sulfathiazole and $2 75 for 100 tablets of sulfadiazine To put it in other words using pneumonia as an example, in which sulfadiazine has largely replaced sulfathiazole in treatment, at wholesale prices it would cost about $0 40 to treat a patient with pneumonia with sulfathiazole and about $1 40 with sulfadiazine Its cost along with a few of its toxic effects is one of its greatest disadvantages for more widespread use However, regardless of its cost, in this country it has become the drug of choice in the treatment of pneumococcal meningococcal, hemolytic streptococcal, Friedlander's bacillus and certain urinary tract infections As further discussion will bring out, its several disadvantages are more than outweighed by the special merits of the drug

Pharmacology

To reiterate briefly sulfadiazine when administered by mouth is nearly completely absorbed from the intestinal tract within 4 to 6 hours the amount of free drug in the circulating blood diminishing rapidly from the 4th to 6th hour Its relatively slow absorption compared to sulfanilamide along with slower excretion with easy maintenance of a high blood level makes it very comparable from a pharmacological standpoint to sulfapyridine The drug is contained more in the red blood cells than in serum or plasma and it causes no significant drop in CO combining power of the blood Probably the slower rate of excretion and the fact that only about 50 per cent of the drug passes into the body water explains why it is possible to obtain and maintain adequate therapeutic levels of sulfadiazine with more ease than with sulfapyridine or sulfathiazole

More recent studies have shown somewhat irregular absorption due to several factors and somewhat irregular distribution in the tissues of the body These features vary further depending upon oral or parenteral administration of the sodium salt and the use of alkalies promoted to decrease the incidence of rénal toxic effects Sulfadiazine orally yields higher concentrations of the free drug in the blood and smaller proportions of acetylated drug in the blood and urine than do

sulfapyridine or sulfathiazole Between 15 and 30 per cent is conjugated Sulfadiazine is absorbed poorly from the stomach and duodenum As pointed out by Peterson and Finland sulfadiazine is absorbed more slowly but more completely when given after a meal than if it is given on a fasting stomach Alkali, when given with sulfadiazine after a meal appears to increase the amount of drug absorbed On an empty stomach however sodium bicarbonate hastens absorption but does not increase the amount absorbed For rapid absorption Loughlin and his co workers [4] point out that the sodium salt by mouth is better than the acid salt with alkali They state further that sodium bicarbonate with sulfadiazine makes for more conjugation than with the acid salt alone and the greatest acetylation occurs with sodium sulfadiazine Acetylsulfadiazine is more soluble in urine than the acetylated derivative of sulfapyridine or sulfathiazole

The labor of pregnancy also has an effect on the absorption of sulfadiazine from the gastrointestinal tract Speert [5] found that during labor in 5 pregnant cases 5 gm of the drug produced a blood level of only 1 3 mgm per 100 c c in 2 to 4 hours whereas in the same patients after labor 5 gm gave a blood level 5 5 times as high This finding suggests that when prompt therapeutic action is required during labor the drug should be given parenterally

When 3 to 4 gm of sulfadiazine are given orally a blood level of 5 to 8 mgm per 100 c c will result in 4 hours The sodium salt by mouth is well tolerated and also gives satisfactory blood levels when given in the fasting state [6] but the fact that it may be necessary to give the sodium salts directly into the duodenum in order to get more rapid absorption than when the free sulfonamides are given has caused the Council of Pharmacy and Chemistry to withhold acceptance of the use of sodium sulfadiazine by mouth [7] With either sulfadiazine or the sodium salt there is no exact linear relationship between dosage and blood level The blood level varies in different individuals given the same dosage but for that individual if complications do not develop the concentration of free drug and the degree of conjugation remains more or less constant i e neither tends to increase with prolonged administration Regardless of the duration of treatment with sulfadiazine when the drug is withdrawn the blood level falls rapidly in 24 to 48 hours to become practically zero in 72 hours Sulfadiazine diffuses readily into pleural and peritoneal fluids but the concentration in the thecal space varying from 50 to 80 per cent of that in the blood rises slowly In the determination of sulfadiazine in aspirated fluids the same care with novocain needs to be exercised as with the other sulfonamide compounds

The method of determination of sulfadiazine in blood urine body fluids and so on is essentially the same as for the other compounds This is discussed in the section on Assay of the Sulfonamide Compounds

The sodium salt of sulfadiazine has enjoyed widespread use particularly for

the initial dose in patients severely ill with an infection amenable to this drug Its use is similar to that of the sodium salts of the other sulfonamide compounds When used intravenously, sodium sulfadiazine has at least one distinct advantage over the sodium salts of sulfathiazole or sulfapyridine in that it is excreted more slowly For this reason a very sick patient may be treated by an initial large dose followed by injections of 2 to 4 gm every 8 or 12 hours with the maintenance of an effective blood concentration With the sodium salt, intravenously or sub cutaneously there are unpredictable variations in the blood level Ratish and his co workers [9] made an interesting observation that whereas a 5 per cent solution of sodium sulfadiazine intravenously gives a high blood level quickly 16 to 24 mgm per 100 c c by giving it in less concentrated solution 0 5 to 1 0 per cent as a slow, steady infusion the blood level does not seem to decline as rapidly as with a single injection of a 5 per cent solution The 0 5 per cent solution of sodium sulfadiazine may be used for subcutaneous administration Its absorp tion is somewhat slower 5 gm in a 1,000 c c clysis giving an adequate blood level of 7 to 8 mgm per 100 c c in four to six hours It has been found to be well tolerated by infants and children [95] Jorgensen and Greeley [10] have given it in as high as 5 0 per cent strength in infants subcutaneously and claim no tissue injury Fox has suggested the sodium salts for local application since he found that its moderate alkalinity caused little tissue irritation, but little use has been made of it A calcium salt of sulfadiazine has been developed particularly for subcutaneous administration[54] In 1 to 5 per cent strength it has a pH of 8 1 to 8 5 only slightly lower than comparable strengths of the sodium salt In 4 per cent solution (pH 8 4) it seems to be tolerated fairly well subcutaneously Except that it can be given in somewhat larger doses by hypodermoclysis it does not appear to offer unusual advantages over sodium sulfadiazine Sulfadiazine has become promising in its local application in the treatment of burns particularly in the form of Pickrell s solution discussed in Part VIII of this chapter This method of treatment is discussed further under the treatment of burns in that same part By this method of application there is relatively little absorption unless the areas involved are very large and extensively denuded Then absorp tion can be appreciable even toxic

Sulfadiazine has been used quite extensively intraperitoneally both experi mentally and clinically It is rather slowly absorbed from the peritoneal cavity in both dogs and man Its absorption is slower than either sulfanilamide or sulfathiazole somewhat more rapid in man than in the dog[3 1] however and pro ducing much greater local reaction than the other two drugs[10] Its rate of dis appearance from the blood after intraperitoneal implantation as with oral admin istration is considerably slower than that for the other sulfonamides An idea of its slow absorption and slow excretion following intraperitoneal administration

with persistence in the blood stream may be gained by stating that whereas no significant traces remain after 5 gm orally intravenously or subcutaneously after 48 to 72 hours appreciable absorption from the peritoneum is still evident after 216 to 572 hours[301] In man the delay in the peak blood level depends upon the dose 5 gm causing a peak of 2 2 mgm per 100 c c in 13 hours 20 gm a peak of 18 5 mgm per 100 c c in 28 hours In the pleural cavity sulfadiazine likewise has been found to be absorbed more slowly and to cause more tissue reaction than sulfanilamide or sulfathiazole[304] Upon intracranial implantation Hurteau[419] found that sulfadiazine caused very little foreign body reaction in fact less than is caused by clips or utures When in contact with cerebral parenchyma it causes no neural destruction or glial reaction but it does give a slight foreign body reac tion in the meninges In the brain it seems to exercise no untoward effect upon the final result of wound healing Applied locally in an ointment to the eye the sulfadiazine level in the aqueous humor has varied between 0 7 and 3 0 mgm per 100 c c By iontophoresis significant bacteriostatic amounts enter the human eye particularly when a corneal ulcer or abrasion is present With usual admin istration the aqueous concentration in the eye averages 55 to 75 per cent of that of the blood[30] Sulfadiazine in starch solution as a rectal enema seldom gives blood concentrations over 1 0 mgm per 100 c c After full therapeutic dosage by mouth only a trace is found in the saliva whereas when incorporated in paraffin and chewed it leads to appreciable concentrations in the saliva

By whichever method sulfadiazine is administered that which reaches the blood stream is retained there with lessened excretion by the kidneys This is one of its advantages ease of maintenance of a satisfactory blood level With oral administration the average patient conjugates about 30 per cent of the drug when given sulfadiazine and about 23 per cent after sodium sulfadiazine The variations have been found to be 15 to 50 per cent [98] There is no tendency for the degree of conjugation to increase with prolonged administration The pro portion of conjugated drug following intravenous administration is less than that following oral therapy generally less than 5 per cent of the total Rarely is it as high as 30 per cent Again there is no increased conjugation with prolonged intravenous administration The amount excreted by the urine totals 45 to 85 per cent average being about 60 per cent of the total administered The solu bility of sulfadiazine and its acetyl salt in the urine much like sulfathiazole is minimum in the usual pH range of freshly voided urine 5 6 to 6 6 This is the range at which renal precipitation is most ap to occur which is discussed more fully under toxic effects of sulfadiazine From a pharmacological standpoint it is important to appreciate that in the pH range of 7 0 to 7 5 the solubility i doubled and even trebled and at a pH of 8 0 it is increased nearly ten fold[3, 308] This is brought about readily by admini tering alkalies such as sodium bicar

bonate not dose for dose with sulfadiazine but in quantities sufficient to produce the desired urinary pH The administration of alkali with sulfadiazine also increases its ionization thereby increasing its bacteriostatic efficacy, for Fox and Rose's studies[109] make it appear that it is the ionized portion of the sulfonamide acids that exert an antibacterial action They attribute the increased efficacy of sulfadiazine among other things, to its more complete ionization at the pH of body fluids than is shown by the other sulfonamide compounds In its bacteriostatic effect sulfadiazine is most comparable to sulfathiazole[310] Since the degree of ionization may be increased by the simultaneous administration, within limits of alkalies and its absorption increased under certain conditions as already discussed this suggests that the use of sodium bicarbonate may increase the therapeutic benefit of sulfadiazine as well as prevent crystalluria and renal complications In the excretion of sulfadiazine and its acetyl salt crystals may appear in the urine whether alkalies are administered or not Such crystals are somewhat different in shape from the simple forms obtained by crystallizing the drugs from water or even from normal urines They have been photographed and described as shocks of wheat with eccentric bindings and shell forms Free sulfadiazine crystals may take on the form of globules and needle like processes the shock of wheat and shell forms being chiefly acetylsulfadiazine Both forms may occur in the same urine[311] Lehr and Antopol believe they are specific enough to be recognized under the microscope, thereby not requiring extensive chemical analysis

Methods of Administration and Dosage

As with the other sulfonamide compounds sulfadiazine may be administered orally intravenously intramuscularly subcutaneously and locally Its rectal administration has not proved satisfactory or even necessary

Sulfadiazine *by mouth* is the method of choice in the average infection in which the patient is conscious and not vomiting Sulfadiazine is supplied in tablets of 0 5 gm (gr 7½) and 0 25 gm (gr 3¾) for oral use The dosage may be computed on a basis of body weight 0 1 to 0 15 gm (gr 1½ to 2) per kilogram per day A usual method is to administer 5 0 gm (gr 75) in the initial dose followed by 1 0 gm (gr 15) every four hours or 1 5 gm (gr 22½) every six hours until the fever subsides This dosage by mouth will give blood levels of the drug between 8 and 15 mgm per 100 c c Larger doses may be used without necessarily encountering untoward effects on the other hand smaller doses than those given above frequently are sufficient depending upon the type of infection being treated and the blood level attained Wheeler according to Plummer[11] has used increasing dosage to attain blood levels in man as high as 25 and 50 mgm per 100 c c

Fortunately none of his cases showed any reactions, neither did they show any improved response from their infection.

In general, however, with sulfadiazine as with the other sulfonamide compounds it is best to strike hard and quickly at the beginning, then withdraw rapidly after the patient recovers sufficiently. After subsidence of the temperature to normal for two to four days it is best to stop the drug abruptly.

For children a satisfactory scheme for oral dosage consists of 0.5 gm. (gr. 7½) as the initial dose followed by 0.25 gm. (gr. 3¾) every 6 hours for infants under 6 months of age; for 6 months to 3 years, 1.0 gm. (gr. 15) initially followed by 0.5 gm. (gr. 7½) every 6 hours; for from 3 to 10 years, 2.0 gm. (gr. 30) initially and 1.0 gm. (gr. 15) every 6 hours. In children, too, remarkable results can be obtained frequently with smaller doses such as 0.5 gm. (gr. 7½) 3 or 4 times a day.

For *parenteral administration* the 5 per cent. sodium salt of sulfadiazine is preferred. Its use is favored (a) in severe infections where adequate and even high blood levels are desired to be attained quickly, (b) in patients who are vomiting and who need the drug, (c) in instances where it is found that sulfadiazine is not being absorbed adequately from the digestive tract, (d) in patients who have undergone surgical procedures of the upper gastrointestinal tract where the drug by mouth may be contraindicated. On the basis of body weight it may be given as 0.1 gm. (gr. 1½) per kilogram as an initial dose. Usually it is sufficient, however, to give 5.0 gm. (gr. 75) as the initial dose dissolved in distilled water or physiological saline in 5 per cent. strength (5.0 gm. in 100 c.c.) given slowly into the vein. This method gives an immediate and high blood concentration, 12 to 20 mgm. per 100 c.c.

It may be added that the sodium salts of the sulfonamides are not as soluble in saline as they are in water. Further, if one uses glucose solution, one should not permit it to boil in the presence of the drug because the glucose inactivates the drug by combining with it to form a compound that is inactive when administered parenterally. If it is desired to continue with intravenous administration, 2.0 gm. (gr. 30) every 8 to 12 hours usually is sufficient. It is advisable, however, to revert to oral administration with a maintenance dose, 1.0 gm. (gr. 15) every 4 to 6 hours, as soon as is feasible to do so. The 5 per cent. solution of sodium sulfadiazine should never be poured into a blood transfusion bottle either preceding, during or after a transfusion; blood clots are apt to result.

As with sulfapyridine and sulfathiazole it has been found that sodium sulfadiazine may be administered *subcutaneously*. It is tolerated well. At first concentrations of 0.3 to 0.8 per cent. were recommended, but it has been found that 2.0 per cent. is well taken. The preferred strength is 0.5 per cent. (5.0 gm. dissolved in 1,000 c.c. distilled water) permitted to run in slowly. The sodium salt

should not be dissolved in sterile isotonic solutions of sodium chloride or dextrose for subcutaneous use In a fairly comprehensive study of the subcutaneous method of administration Taplin and his associates[413] sterilized the 0 5 per cent solution by heating and observed no untoward effects They preferred the method of adding the salt to the vehicle heating to the boiling point, cooling to body temperature and then administering it subcutaneously to the alternative of heating the vehicle first then adding the salt and cooling The former method seemed more convenient In continuing this method of administration 2 0 gm every 8 hours will give an adequate blood level of 8 to 15 mgm per 100 c c The intravenous and subcutaneous routes may be used together

For *intramuscular* injection sodium sulfadiazine may be given in 25 to 33 per cent strength A convenient method is to dissolve 7 5 gm in 25 c c sterile distilled water From this stock solution 3 to 5 c c may be administered deeply into the upper outer quadrant of the buttock every 4 to 6 hours It causes very little burning and no local reaction This method gives an adequate blood level of 9 to 15 mgm per 100 c c

The *local use* of sulfadiazine has found its greatest application in man in intraperitoneal implantation and in the treatment of burns The treatment of burns with this drug is considered in another part of this chapter Intraperitoneally it has been used in doses from 5 to 20 gm of the powdered drug sprinkled lightly over the serous surface As mentioned previously it is absorbed slowly and causes considerable local tissue reaction In the final analysis it does not seem to offer any advantages over the much more soluble and less irritating sulfanilamide In fact when one of the sulfonamides is indicated for local application the present practice is to use sulfanilamide as a powder locally and to give sulfadiazine orally for its systemic effect This has the advantage over sulfanilamide alone in the maintenance of an adequate blood level Although the sodium salt has been advocated for local use, it had best not be introduced into a serous body cavity The intrathecal use of sulfadiazine or sodium sulfadiazine also is not recommended

So far in the use of sulfadiazine no medication or food has been found which cannot be given to patients receiving this drug

Variations in dosage and routes of administration preferred under certain circumstances will be discussed in the consideration of the various infections which follows

Clinical Uses of Sulfadiazine

Since its introduction in 1941 sulfadiazine has become the drug of choice in the treatment of many infections There have been many competent opinions

expressed to the effect that among the sulfonamides in common use in this country today sulfadiazine serves all the needs of systemic sulfonamide therapy as satisfactorily as any other surpasses them in some infections and except for renal complications is by and large more free of toxic effects In its absorption distribution and excretion it is similar to sulfapyridine but in its bacteriostatic effects it is about the same as sulfathiazole It has a bacteriostatic action upon a wider variety of organisms than either sulfanilamide sulfapyridine or sulfathiazole Sulfadiazine has been accepted by the Council of Pharmacy and Chemistry for the treatment of infections due to the pneumococcus hemolytic streptococcus meningococcus Friedlander s bacillus staphylococcus and gonococcus and in the urinary tract *E coli* *Aerobacter aerogenes* and staphylococcus That does not indicate necessarily that sulfadiazine is the drug of choice in these conditions for the present evidence still favors sulfathiazole in staphylococcal and gonococcal (urethritis) infections and the results are about equal in the ordinary types of urinary tract infections In bacteremias it is the drug of choice against the hemolytic streptococcus and Friedlander s bacillus but with other organisms such as staphylococcus aureus and the colon bacillus sulfathiazole and sulfadiazine are about equal In bacteremias due to the pneumococcus gonococcus and streptococcus viridans sulfapyridine sulfathiazole and sulfadiazine are about equally effective All four drugs sulfanilamide and the above three have about the same ability to clear the blood stream other factors being equal in bacteremia due to the meningogoccus [14] When the infecting organism is not known sulfadiazine should be chosen In bacteremias large doses of the drug preferably intravenously with maintenance of a high blood level 10 to 20 mgm per 100 c c are to be used

The wide variety of organisms against which sulfadiazine is effective is shown in Table X The drug is particularly effective against those organisms and their respective diseases shown in italics It will be noted that many of the organisms and diseases listed are contained also in the lists given with the other sulfonamide compounds Hence it becomes often a matter of choice which drug to use under given circumstances It does not mean that sulfadiazine is to be used to the exclusion of sulfanilamide sulfapyridine and sulfathiazole Each has a place

In *bacillus coli* infections whether in the blood stream or in the urinary tract sulfadiazine with blood levels of 5 to 10 mgm per 100 c c has proved very effective If suppuration has occurred drainage prior to the institution of sulfadiazine gives the best results In arthritis due to this organism sulfathiazole probably is slightly more effective but sulfadiazine is preferred by Bauer and his associates[8] because of lower toxicity

In some of the original work on sulfadiazine Bliss and her co workers [16] and Hawking[17] found that this new compound and sulfathiazole locally were both

TABLE X

INFECTIONS IN WHICH SULFADIAZINE IS EFFECTIVE*

Aerobacter aerogenes	*Pneumococcus*
urinary tract infections	*arthritis*
B coli	meningitis
arthritis	*pneumonia*
urinary tract infections	Proteus vulgaris
Cl epticum	*urinary tract infection*
Cl welchii	Pseudomonas pyocyanea
Friedlander s bacillus	*urinary tract infection*
pneumonia	Staphylococcus
Gonococcus	meningitis
arthritis	urinary tract infection
conjunctivitis	*Hemolytic streptococcus B*
urethritis	*arthritis*
H influenzae	*bacteremia*
meningitis	*cellulitis*
Meningococcus	*erysipelas*
arthritis	*mastoid*
endocarditis	*meningitis*
meningitis	*otitis media*
otitis media	pharyngitis (deep)
septicemia	*pneumonia*
	puerperal sepsis
	scarlet fever (complications)
	septicemia
	inusitis
	Streptococcus viridans (enteral)

* Disea es and bacteria in italics are those in which ulfadiaz ne is especially effective

effective in the control of infections in mice produced by the intramuscular injection of *Cl welchii* or *Cl septique* but both authors added that sulfadiazine was no better than and probably inferior to sulfathiazole for broad usefulness against various gas gangrene organisms On the other hand, in dogs Sewell Dowdy and Vincent[318] found sulfadiazine superior to other sulfonamides in the treatment of experimental gas gangrene When sulfadiazine was combined with roentgen irradiation the survival rate in rabbits was lower than with either drug or irradiation alone Sewell and associates[318] and Halford[319] have observed good response in humans There are several reports of the beneficial results of any one of the sulfonamide compounds locally in the prophylactic treatment of gas gangrene but the present trend seems to be the use of sulfanilamide locally and promptly in aerated wounds with the addition of polyvalent gas gangrene antitoxin combined with sulfathiazole or sulfadiazine by mouth Perhaps penicillin will prove to be more effective in the treatment of gas gangrene in humans than the sulfonamide compounds have been

Infections in mice due to the *Friedlander bacillus* (type B) have been found to respond satisfactorily to sulfadiazine One human patient with type B pyelonephritis and liver abscess treated with this drug by Finland Peterson and Goodwin died[3 0] However two cases with pneumonia due to type A of this organism responded excellently to the drug with an average dose of 135 gm The reported results are few and somewhat variable

Sulfadiazine appears to be the first of the sulfonamide compounds offering some encouragement in the treatment of *H Influenzae* infections particularly meningitis Early in the history of this drug Trevett [1] treated two cases of this disease and both died But subsequently Sako and associates[3] Feldman and associates[3 1] and Winters and Greenthal[3] have reported 11 cured cases out of 15 treated Three of Sako and his associates cases were cured on sulfadiazine alone but all the others received influenza antiserum in addition All of these authors advocate the combined treatment Stupor and coma under such a regime are seen to disappear in 36 to 48 hours and the spinal fluid cultures may become sterile in 5 to 7 days Because the mortality rate in this disease always has been very high 95 to 100 per cent blood levels of 20 mgm per 100 c c and spinal fluid levels of 10 to 15 mgm per 100 c c are necessary to obtain the desired results Alway and Platou advocate the administration of the sulfadiazine in saline by continuous intravenous drip For this sodium sulfadiazine should be used After apparent cure it is safest to continue the patient on sulfadiazine by mouth for an additional two weeks

The *meningococcus* is particularly susceptible to the bacteriostatic effect of sulfadiazine In bacteremia due to this organism (meningococcemia) the bacteria may be cleared from the blood stream in 24 to 48 hours with blood levels of 8 to 10 mgm per 100 c c In this circumstance it is wisest to give the initial dose intravenously with the sodium salt followed by oral doses of sulfadiazine as the occasion will allow The average total dose required is 45 to 50 gm In arthritis due to the meningococcus sulfadiazine is the drug of choice

It is in *meningococcus meningitis* that sulfadiazine has shown its greatest worth It has brought a previous mortality of about 40 per cent down to a present figure between 3 and 10 per cent Dingle and Finland have compared the results of treatment of meningococcus meningitis with all the sulfonamide compounds In a review of over 1 000 patients they found the mortality to be 14 per cent for those treated with sulfanilamide alone 25 per cent for those treated with sulfanilamide and antiserum 8 per cent for those treated with sulfapyridine alone and 12 per cent for those treated with sulfapyridine and serum The fact that sulfathiazole has been found to diffuse with difficulty into the cerebrospinal fluid has perhaps prevented its use in any large series of cases of meningitis Isolated reports exist however in which cases of meningococcus meningitis were

cured with usual doses of sulfathiazole No statistics of these were found for comparison in the present discussion In 248 cases treated with sulfadiazine alone, reviewed by the author, there were 7 deaths, a mortality of 2 8 per cent This excellent result among other things has prompted the Committee on Chemotherapy of the National Research Council to recommend sulfadiazine to the Armed Forces as the drug of choice in the treatment of not only meningococcal but also hemolytic streptococcal and pneumococcal meningitis In the few failures that have occurred lag in the institution of treatment has been an important factor In those cases that have had prompt and adequate treatment and yet succumbed with the spinal fluid becoming cleared of organisms it seems fair to believe that the bacteriostatic effect of the drug was adequate, but its action was ineffectual against whatever toxins had been formed by the organisms while the disease was getting under way

Much of the success in the treatment of meningococcic meningitis is in recognizing the 'spotted fever' of meningococcemia and the signs of meningeal irritation if the disease has advanced that far so that treatment may be begun early enough If the meningococcic infection is recognized before the signs of meningitis are present, adequate therapy with sulfadiazine will cause complete recovery In the diagnosis of meningococcic meningitis smears and cultures of spinal fluid may be negative after sulfadiazine has been started, even if p aminobenzoic acid has been added to the culture medium Although somewhat less intensive treatment may be instituted if the patient does not appear very ill, it is advisable to give 5 gm as the initial dose either as sodium sulfadiazine in 100 c c distilled water or saline or intramuscularly as a 25 per cent solution 5 gm in 20 c c distilled water The intrathecal administration of sulfadiazine is unnecessary Sodium sulfadiazine should never be introduced into the spinal canal If the patient needs fluid as is usually the case a 0 5 per cent solution, 5 gm in 1,000 c c saline, may be given by hypodermoclysis The initial dose should be followed by 2 5 gm sodium sulfadiazine every four hours either intravenously or intramuscularly for the first 12 hours, when the patient is severely ill For the moderately ill patient a dose of 1 5 gm every four hours will give a blood level of 12 to 16 mgm per 100 c c With improvement or in mild cases after 24 hours the dose may be reduced to 1 0 gm every four hours day and night *With this regime* it is desirable to obtain the first blood level after 12 to 16 hours not only to guard against excessive levels and resulting toxic effects but more important, to insure that an adequate blood level is being attained Fluids should be forced, particularly with the intravenous use of sodium sulfadiazine to levels of 3 000 to 4 000 c c per 24 hours to insure a urinary output of 1 500 c c per 24 hours Fluids may be given in part intravenously the remainder subcutaneously When consciousness is regained water by mouth is preferred If sedation is required for

severe restlessness paraldehyde per rectum 20 to 30 c c or nembutal intramuscularly 0 1 to 0 2 gm (gr 1½ to 3) usually will suffice

With intensive treatment a determination of blood level of the drug complete blood count and urinalysis should be made daily On this regime the temperature should begin to decline in 48 to 72 hours consciousness be regained and the spinal fluid begin to clear The total amount of drug required for the entire treatment is about 75 gm Treatment safely may be terminated abruptly one week after the patient is asymptomatic

A question frequently raised in the treatment of meningitis with the sulfonamide compounds is when and how often should a spinal puncture be performed? Although dogmatic statements cannot be made on the basis of the evidence it seems reasonable to employ lumbar puncture in all cases for diagnosis and at other times only when there are definite indications such as signs of continued increased or increasing pressure or to determine progress in a doubtful case Frequent lumbar punctures should be avoided and forced spinal drainage need never be employed Hodes and Strong [6] recommend a routine tap on the twelfth day of treatment By this time in the vast majority of cases the spinal fluid will be perfectly clear although in three cases under the writer s observation as many as 30 to 60 cells were still present one and two months after adequate treatment and good recovery but no organisms could be recovered

Another question frequently raised is whether or not to give antimeningococcus serum in addition to sulfadiazine Usually it is not necessary In an analysis of 3 575 cases by Beeson and Westerman[3 7] in which sulfonamide compounds but not sulfadiazine had been used there was no indication that the addition of antimeningococcic serum to the therapy was of direct benefit It is the present opinion of Dingle and Finland that patients who have received full doses of sulfadiazine with adequate blood and spinal fluid levels and yet fail to show significant improvement after 48 hours should receive antiserum During this time the organism can be isolated and typed or grouped in the laboratory and an antiserum selected which contains antibodies not only for the same group but against the patient s own strain as indicated by agglutination capsular swelling or some other immunological reaction If antiserum is used it should be given intravenously and in large doses

Of interest in connection with epidemic meningitis are several recent studies on the *prophylactic use* of sulfadiazine against the meningococcus Cheever at the Naval Medical Center [8 9] studied 1 004 cases with throat cultures and found 57 per cent positive for the meningococcus Forty six per cent of these were type I Out of 203 selected cases 161 were carriers He placed the 161 on sulfadiazine 3 0 gm (gr 45) the first and second days 2 0 gm (gr 30) the third day and after that time all throat cultures were negative After a total of 144 hours one

carrier had recurred In 186 untreated controls 25 per cent became negative spontaneously in one week, the rest remained positive In another study Mueller[3] used 400 individuals, 200 given sulfadiazine for 3 days 3 0 gm on the first day and 2 0 gm on the second and third days The remaining 200 served as controls Three days after the cessation of therapy all throats were cultured again and the carriers in the control group had increased from 68 to over 70 per cent Of the 200 who had received sulfadiazine not one showed any meningococci After a further lapse of three weeks cultures were obtained on 116 of the treated cases and of these 18 or 16 per cent again showed meningococci, type I If such figures can be confirmed the administration of sulfadiazine by mouth during an epidemic or threatened epidemic may serve a very useful purpose since quarantine on a large scale usually is out of the question

As a further prophylactic measure it seems rational and perfectly safe in treating patients subjected to mastoidectomy to institute chemotherapy 12 to 24 hours before operation and to continue it in full doses for a few days In some cases meningitis undoubtedly will be prevented by such a routine In otitis media itself due to the meningococcus sulfadiazine in average doses by mouth has proved to be very effective Again as with the other sulfonamide compounds discussed in this condition sulfadiazine too may have a masking effect and cause unnecessary delay when operative intervention is indicated on the mastoid

The *pneumococcus* particularly when it invades the pulmonary tissues is very susceptible to sulfadiazine It is the drug of choice in arthritis due to this organism[315] The picture still is somewhat discouraging however in the case of *pneumococcus meningitis* Originally Steel and Gottlieb[131] reported 60 per cent recoveries in collected series of patients treated with sulfanilamide or sulfapyridine with and without specific serum In a more critical analysis Dowling and his co workers[33] found only 4 recoveries in 67 cases treated with the sulfonamides One of these had received sulfadiazine and serum and recovered In 8 cases reported by Finland and his associates[130] receiving both sulfadiazine and serum 3 recovered one with bacteremia It is the conservative opinion of this group[130-31] that the more correct mortality rate in this disease treated thoroughly with one of the sulfonamides and all other available methods of treatment including serum is in the vicinity of 80 per cent It is probably fair to state however, that the use of one of the sulfonamides is directly responsible for most of the recent recoveries Patients who exhibit no other focus of infection and who have many cells with few organisms in the cerebrospinal fluid have a better prognosis With many organisms and few cells in the spinal fluid the prognosis is poor The type of infecting pneumococcus seems to have little effect[33] The treatment should consist of sulfadiazine in large doses beginning with the sodium salt intravenously with maintenance of a blood level of 15 to 20 mgm per 100

c c and a spinal fluid level of 12 to 15 mgm per 100 c c Since therapeutic rabbit sera are now available for all types of pneumococci specific antiserum should be given to all of these cases intravenously as soon as the type of organism can be determined

In 1938 about the time that sulfapyridine was found to be effective in the treatment of *pneumococcus pneumonia* the death from this disease was 50 6 per 100 000 population For 1942 the figure is 29.4 [3] There is no doubt that this significant decline may be attributed to the newer chemotherapeutic agents and to serum therapy That most of this reduction is the result of sulfonamide chemo therapy is brought out rather strikingly by the studies of Flippin Schwartz and Domm [4] which showed that over a 5 year period 1 635 cases of pneumonia treated with sulfapyridine sulfathiazole or sulfadiazine had a mortality rate of 10 6 per cent as against 40 1 per cent in 1 904 cases over a 5 year period treated before these drugs were used Furthermore serum treatment is not used very much today

In these results sulfadiazine has played its part but not to the exclusion of the other two drugs For although sulfadiazine has become the drug of choice in the treatment of this disease when viewed from a mortality statistical standpoint alone it has proved to be no better than sulfathiazole or sulfapyridine but it has become the drug of choice and perhaps correctly so chiefly because of the ease of administration of the lack of such toxic effects as nausea and vomiting of an adequate blood level easily maintained and of the consistently good therapeutic results As brought out in previous sections a review of 25 000 cases treated with sulfapyridine showed a mortality rate of 8 87 per cent However sulfapyridine now is seldom used in this disease unless it alone is available or the patient has not responded to sulfathiazole or sulfadiazine The most important objection to sulfapyridine has been the nausea and vomiting it provokes In a review of 1 400 cases treated with sulfathiazole the general mortality was 7 6 per cent and similar to sulfapyridine somewhat lower for younger individuals and some what higher for the older age groups The two chief disadvantages to sulfa thiazole have been the difficulty in maintaining an adequate blood level and the frequency with which it produces drug fever to complicate the clinical picture Because of these shortcomings sulfadiazine has more or less replaced them In a comparable study which the writer has made of series of cases of pneumococcus pneumonia treated with sulfadiazine a total of 1 850 cases showed a general mor tality of 9 56 per cent a figure very comparable to *sulfapyridine and sulfa* thiazole with extremes of 0 9 per cent for children and 42 3 per cent for indi viduals over 60 years of age With a bacteremia of course the mortality is higher from 30 to 35 per cent It is felt that a mortality rate of 8 to 10 per cent in properly treated cases comes near to being an irreducible minimum since there

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is always a certain percentage of cases in which treatment is started late, a certain percentage with complications such as endocarditis or with overwhelming infections and particularly in the older age groups a certain number with coincident chronic diseases such as heart failure kidney insufficiency diabetes, and so on, in all of which specific therapy as available at present often is ineffective

In the treatment of pneumococcus pneumonia with sulfadiazine the drug may be given orally or intravenously The intravenous route using sodium sulfadiazine, is preferred in patients who are comatose, who are severely ill, or who have a bacteremia Drug for drug intravenous sodium sulfadiazine produces no better results in this disease than when adequate blood concentrations can be attained by the oral administration of sulfadiazine [34] It is fair to add however, that patients receiving sodium sulfadiazine intravenously although showing a similar incidence of critical fall in temperature regain the normal temperature at a somewhat slower rate In the seriously ill or comatose patient 3 0 to 5 0 gm as the initial dose in the form of a 5 per cent solution in distilled water intravenously followed by 2 0 gm every 12 hours will give blood levels of 10 to 18 mgm per 100 c c When the oral dose can be administered, 1 0 gm every 4 to 6 hours will maintain a blood level of 8 to 12 mgm per 100 c c

In the average adult moderately ill with pneumococcus pneumonia, sulfadiazine by mouth o to 3 0 gm initially followed by 1 0 gm every 6 hours usually will cause the temperature to fall in 48 to 72 hours with rapid clinical improvement An optimum blood level does not exist in the treatment of this disease but levels of 5 to 10 mgm per 100 c c usually are sufficient when properly maintained A total average of about 30 gm of drug over a period of 6 days usually is adequate During the treatment fluids should be forced a high caloric diet given and oxygen supplemented if necessary Good nursing care still is of paramount importance in this disease When complications arise they should be dealt with promptly In the uncomplicated case after the temperature has returned to normal for 48 to 72 hours the drug is to be stopped abruptly

In the consideration of the dosage of sulfadiazine in the treatment of pneumococcus pneumonia several recent studies are of considerable interest Larger doses than the ones described above have not given significantly better results[35] On the other hand smaller doses are frequently just as effective Dowling and his associates [46] treated 160 patients with pneumonia with very large and with rather small doses In 81 cases given 2 0 gm initially followed by 0 5 gm every 4 hours the results were practically as good as in 79 cases given 6 0 gm initially followed by 1 0 gm every 4 hours The three slight advantages shown by the patients receiving the larger doses were (a) a slightly more rapid drop in temperature (b) slightly fewer days in the hospital and (c) perhaps fewer complications The mortality rates were comparable In work begun originally to

study the prognosis in pneumococcus pneumonia Frish Price and Myers[336,337] have recommended an approach to sulfonamide dosage in this disease that is relatively *unique and* at the same time profoundly simple Their cases were divided *into four groups depending upon the number of pneumococci seen per oil immersion* field in the examination of the sputum Group A contained 10 or less pneumococci per field group B 11 to 30 group C 31 to 75 and group D over 76 organisms Since their original studies seemed to show that the outcome of the disease was related more closely to the sputum count than to the type of pneumococcus *the presence or absence of bacteremia* the duration of the disease or often *even the extent of consolidation they were able to evaluate the results of therapy* on this basis alone In general they found that patients with sputum counts less than 30 do well regardless of treatment except when they are older individuals or with more than one lobe involved In fact most patients with less than 10 organisms per field get well without any treatment With large numbers of *organisms intensive treatment is required* because usually it means several lobes *involved low resistance and bacteremia With these principles established* the authors recommend that where there are 11 to 20 organisms per high power oil immersion field in the sputum sulfadiazine in doses of 2 0 gm initially followed by 0 5 gm every 4 hours will bring about the desired results When the sputum count is 21 to 35 4 0 gm initially and 1 0 gm every 4 hours should be given Thirty six to 50 organisms call for large doses such as the sodium salt intravenously *5 0 gm initially and 2 0 gm every 12 hours When there are more than* 50 organisms in the *field* serum may be administered *in addition but in patients* with such high counts it seems to contribute insignificantly toward recovery They likewise point out that when dosage is regulated according to the sputum count done daily excellent end results may be obtained with less than the customary amount of chemotherapy

In any of the dosage schemes which have been presented it should be emphasized that the use *of sodium sulfadiazine intravenously enhances the formation* of urinary calculi and hence makes renal toxic effects more frequent Therefore large amounts of fluids and alkalies as discussed under renal toxic effects of sulfadiazine should be administered Ordinarily blood levels should be determined frequently to be sure that the patient is receiving enough of the sulfonamide not entirely as a check on toxicity Furthermore patients who are markedly dehydrated or have primary renal disease or congestive heart failure should have blood *determinations done once a day since they are subject to rapid accumulations of the drug*

On the above therapy with sulfadiazine the clinical response is good in over 90 per cent of the cases when treatment is started early When drug therapy is instituted in the first four days of the disease the mortality averages 6 per cent

as against 25 per cent when treatment is started after the fourth day The mortality in type III because of its excessive production of capsular polysaccharide, still remains high although sulfadiazine is helpful in preventing reticulation[3, 6] In all other types of pneumococcus pneumonia the antibody response of patients, who recover, is the same after sulfadiazine as after sulfapyridine or sulfathiazole, and the same as in patients who recover with specific serum Blood complement activity on the other hand, which may be lowered by antipneumococcus horse or rabbit serum shows no change following sulfadiazine therapy[338] In general a high initial white blood cell count, diminishing rapidly in 48 hours with sulfadiazine is a good prognostic sign, whereas persistence or progression of a high white count indicates spread or a complication If the initial white cell count is low, it may mean serious illness In itself it is no contraindication to sulfadiazine for if the patient responds to the drug the white blood cell count will rise within 48 to 72 hours If a low white cell count fails to rise the outlook is poor

Failure of the patient with pneumonia to recover with sulfadiazine therapy may be caused by (a) pneumonia caused by organisms that do not respond to sulfadiazine (b) improper selection of the drug (c) undertreatment with the drug (d) chemotherapy begun too late (e) drug toxicity, (f) the presence of antisulfonamide substance (g) the failure to employ other therapeutic measures[339] and finally (h) the age of the patient and (i) complicating debilitating disease or one fatal in itself With a few strains of pneumococci with which sulfadiazine had failed sulfonamide resistant strains penicillin in small doses was found to be quite effective when tested in mice[34] What place penicillin may take in the future treatment of pneumococcus pneumonia particularly in cases not responding to the sulfonamides will be awaited with interest

Whether or not to administer type specific serum in addition to or in place of sulfadiazine still is a controversial question Usually it is not necessary In certain instances however, benefit may be derived It seems reasonable to recommend its use when the patient is unable to tolerate sulfadiazine when drug resistance is demonstrable or when the patient fails to respond to chemotherapy Lack of response when the pneumonia is due to the pneumococcus may be said to be present after 72 hours of sulfadiazine treatment with no effect When serum is to be administered, the usual preliminary conjunctival and intradermal sensitivity tests always should be performed If the results are negative after o minutes 1 o c c of undiluted serum may be administered intravenously as a further test dose If after another hour no untoward effects have been encountered 100 000 units of type specific undiluted serum, warmed to body temperature should be given intravenously followed by further injections of serum when necessary If reactions occur with the smaller test doses the prolonged desensitizing procedure must be carried out

Repeated attacks of pneumococcus pneumonia tend to occur in approximately 15 per cent of pneumonia patients Sulfadiazine like sulfapyridine and sulfathiazole seems just as effective when administered for subsequent attacks as during its use in the initial attack[41] There is evidence to suggest that the repeated use of sulfadiazine for recurrent pneumococcus pneumonia does not increase the incidence or severity of drug toxicity In fact in Schwartz s studies mild toxic reactions were somewhat more frequent in the initial administrations of the drug than in the subsequent ones

When the pneumonia is due to the pneumococcus sulfadiazine is administered and the result is very gratifying However it is just as important to know when not to give the drug When the evidence obviously points toward a *virus etiology of the pneumonitis* it is much better to withhold the sulfonamide compounds as they are notoriously ineffective However when one is uncertain it is the present concensus of opinion to give sulfadiazine unless a contraindication exists This may be done until the etiology and the effect of chemotherapy can be evaluated over a period of 48 hours In general there is a tendency today to make a diagnosis of virus pneumonia by exclusion as when no pneumococci can be found or the person has been treated with a sulfonamide such as sulfadiazine and fails to respond In this circumstance as Finland points out there are two things to remember First even the common bacteria that are known to respond sometimes are resistant to the drug Second pneumonia due to organisms such as the streptococcus or the staphylococcus requires prolonged and intensive treatment Hence if one begins with a mild infection that one is attempting to treat with small doses the patient may become suddenly severely ill one may assume then that one is dealing with a virus pneumonitis that has not responded when actually one is dealing with a streptococcal or staphylococcal pneumonia that has been treated inadequately It has been shown moreover that sulfadiazine is effective against the streptococci or staphylococci that may complicate pulmonary influenza [43] The safest procedure when one is uncertain is to treat intensively with sulfadiazine from the very beginning and to continue treatment for 48 to 72 hours no longer while intensive search for causative organisms is carried out If there is no response at the end of that time stop the drug and stop it completely Except for the rather rare instance of sulfonamide sensitivity few patients will react adversely on such a regime The majority of cases of sulfadiazine toxicity are the result of prolonged over 5 to 7 days administration of the drug

Ordinarily the presence of jaundice anemia leukopenia or neutropenia per se in a patient with pneumonia does not contraindicate sulfadiazine therapy if care is taken as these conditions frequently will disappear as the infection is brought under control It is wisest to be extremely cautious and even to withhold the drug

if the patient is known to have had a toxic reaction to previous sulfonamide chemo therapy or to have signs of active renal inflammation or irritation

In simple *acute pharyngitis* and *tonsillitis* sulfadiazine like the other sulfona mide compounds has shown no better results than symptomatic therapy of bed rest salicylates throat irrigations and so on In a study carried out in a military camp[144], consisting of 670 cases of simple respiratory infections (colds, etc) exclusive of tonsillitis and pneumonia there were no significant differences, either in the length of the febrile period or in the period of hospitalization among the group receiving sulfadiazine as compared to a control group treated symptomati cally In cases of *pulmonary abscess bronchiectasis* and *putrid empyema* sulfa diazine may not prove to be very effective

In *staphylococcus infections* sulfadiazine has proved to be effective in some instances but at the present time has not superseded sulfathiazole in the treatment of diseases due to this organism In vitro studies of several strains of hemolytic staphylococci tested by determining by manometric measurements the oxygen consumption and anaerobic carbon dioxide formation of glucose peptone broth cultures, Kempner and his co workers[145] found that sulfadiazine was less effective than sulfathiazole In human patients however where results are not always comparable to studies in vitro Finland and his associates[7, 0] obtained good results in the treatment of 12 cases of pneumonia due to staphylococcus aureus and in 5 cases of staphylococcal sepsis In 2 cases with no response there was failure also with sulfathiazole In childhood sepsis due likewise to staphylococci good results have been obtained[146] The cases of 2 infants are reported who failed to respond to sulfathiazole but did recover with sulfadiazine

In staphylococcal infections particularly as with the other sulfonamides, the bacteriostatic and possibly the bactericidal action of sulfadiazine are inhibited by peptone and p aminobenzoic acid In boils and carbuncles the drug by mouth may be effective with a blood level of 7 to 10 mgm per 100 c c For larger col lections of pus due to this organism drainage should be instituted first In staphy lococcal infections of the urinary tract the drug has proved to be quite satisfactory upon oral administration While sulfadiazine is effective in many cases of staphy lococcus albus and aureus infections sulfathiazole appears to remain the drug of choice

Immediately after the introduction of sulfadiazine as a chemotherapeutic agent it gave promise of being effective in infections due to the *streptococcus* par ticularly the beta hemolytic strains Further observations and extensive clinical trial have demonstrated its efficacy so at the present time it has become the drug of choice in treating infections and diseases due to beta hemolytic streptococcus The reasons for this are several Compared to sulfanilamide, its closest com petitor in these sulfonamide compounds sulfadiazine is not only bacteriostatic

but somewhat bactericidal Secondly is the ease with which an adequate blood level is maintained for with sulfanilamide in its rapid excretion the blood level tends to drop rapidly Thirdly the bacteriostatic and bactericidal effects of sulfa diazine in human blood against the streptococcus are apparent in lower dilutions than with sulfanilamide[3 7] However a recent reinvestigation of the whole sub ject is of interest from a scientific standpoint For Marshall and his co workers [8] restudied and compared the therapeutic activity of 33 sulfonamide derivatives in streptococcal infections in mice When compared on a weight basis that is milli grams per 100 c c of blood none of the derivatives including sulfadiazine was significantly more active than the parent compound sulfanilamide Nevertheless for the reasons given above and for the fact that certain toxic reactions such as cyanosis nausea and vomiting hemolytic anemia leukopenia and so forth occur much less frequently with sulfadiazine than with sulfanilamide sulfadiazine has superseded sulfanilamide very generally in the treatment of streptococcal infec tions Sulfadiazine has one disadvantage over sulfanilamide however and that is its toxic effects on the kidneys Therefore if a patient with a streptococcal infection has any significant urinary abnormality with nitrogen retention or in whom activity of a renal lesion may be provoked by sulfadiazine crystalluria sulfanilamide still is an effective and dependable drug

Like sulfanilamide in streptococcal infections sulfadiazine produces its best results in spreading infections that are deep In localized superficial lesions as pharyngitis it is no better than sulfanilamide Para aminobenzoic acid likewise inhibits sulfadiazine action just as that of the other sulfonamides

The variety of streptococcal infections in which sulfadiazine is effective is as extensive as for sulfanilamide The beta hemolytic streptococcus is particu larly susceptible Finland and his group have published the largest variety of streptococcal infections including septicemia cellulitis erysipelas meningitis pneumonia puerperal sepsis and other diseases in which the results of treatment have been excellent The dosage to employ is as outlined previously in this sec tion using the sodium salt intravenously when indicated otherwise adhering to the oral administration More and more it has been learned that when one is giving the sulfonamides for systemic effect one should strike hard at the beginning of treatment force fluids and maintain adequate urinary excretion then stop the drug abruptly when the desired results have been obtained

Because of its efficacy and relative safety sulfadiazine has become the drug of choice in an infection where a sulfonamide seems indicated and the etiology is not established or is pending the determination of the causative organism For example it is the drug to use in the treatment of meningitis or urinary tract infection until the organism is identified After the causative organism is estab lished a selection of drug may be made

In *diseases of the ear nose and throat* sulfadiazine has become the most popular sulfonamide compound to use As pointed out by Porter[349], the problem of the otolaryngologist in the use of these drugs is somewhat different from that of the internist or surgeon in that higher dosage frequently is required, the problem of adequate drainage presents itself more often, and supplementary measures such as immune serum transfusions and so on remain of considerable importance particularly in children Sulfadiazine, as with the other sulfonamide compounds may produce a masking effect which may lead the physician into a false sense of security regarding mastoid complications and the need for surgery Livingston[350] has offered the rule that if all symptoms have subsided under sulfadiazine except otorrhea and this persists beyond the second week, one should become suspicious of masking Valuable as these drugs are, in order to avoid overenthusiasm Livingston reminds us that, since most acute infections of the ear nose and throat are more or less self limited with a tendency toward spontaneous resolution any therapeutic measures which are instituted are likely to appear valuable but may be only incidental to the natural course of the disease Such reasonable conservatism is warranted always, since so many sprays and gargles made from sulfadiazine are introduced from time to time for the treatment of colds, sinusitis and streptococcal pharyngitis On the other hand that sulfadiazine has produced dramatic results, when used properly in the correct dosage in otolaryngological conditions is attested by the frequency with which mastoid surgery has been prevented The otologist who used to perform a hundred mastoid operations over the winter will now do barely a dozen

In such streptococcal infections as scarlet fever rheumatic fever and infections caused by an oral strain of non hemolytic streptococcus as subacute bacterial endocarditis sulfadiazine has little effect It is active however, against the enteral strain of streptococcus viridans

Sulfadiazine has been tried and with some hope of success in the *prophylaxis of streptococcal infections* particularly scarlet fever and rheumatic fever In an epidemic of streptococcal infections of the respiratory tract in which scarlet fever was endemic Watson and his associates[351] gave either 0 5 gm (gr 7½) at 8 A M and 4 P M or 1 0 gm (gr 15) each morning to 200 cases with no scarlet fever becoming manifest in the treated patients The blood levels during this procedure ranged from 1 5 to 3 7 mgm per 100 c c averaging 2 5 mgm The incidence of toxicity was very low Against scarlet fever itself sulfadiazine has seemed no more effective than the other sulfonamide compounds, but like them it is curative in the complications such as otitis media mastoiditis and pneumonia

In Part IX of this chapter is discussed the evidence for the use of sulfanilamide in the prophylaxis of rheumatic fever that is, not in preventing rheumatic fever as such but in preventing recurrences of streptococcic sore throats which

frequently precede rheumatic fever In a study with children, which Boyer[35] has made at the Massachusetts Memorial Hospitals using sulfadiazine he suggests that there is no reason for supposing that sulfadiazine will prove to be less effective than sulfanilamide The toxic reactions were very slight this suggests further that sulfadiazine will prove to be more useful than sulfanilamide only in so far as a better tolerated drug will benefit more patients

Sulfadiazine has been tried adequately in the treatment of *gonococcus infections* and found to be very effective On a statistical basis alone the three drugs sulfapyridine sulfathiazole and sulfadiazine are about equal with the evidence slightly in favor of sulfathiazole in most series This difference is very slight, however, the average figures for gonorrheal urethritis in the male being approximately 95 per cent for sulfathiazole 90 per cent for sulfadiazine and 85 per cent for sulfapyridine In comparative studies with all the sulfonamide compounds as they have become available Satterthwaite and his associates[658] obtained 95 per cent cures with sulfadiazine a higher percentage of cure than we have been able to obtain with any other sulfonamide Several however have found that with sulfadiazine it takes slightly longer for the discharge to disappear and the two glass urine test to become clear Various outlines of dosage have been recommended often with good results with smaller doses A usual and acceptable procedure is a 5 day course giving 4 0 gm (gr 60) daily for 3 days then 3 0 gm (gr 45) daily for 2 days In a few cases a slight discharge may still be present at the end of that time for which Parsons [4] advises continuation of 2 0 gm (gr 30) for another 3 to 4 days until cure Some authors have advised 4 0 gm (gr 60) daily for 10 days Neither of these alternatives has resulted in a higher rate of cure As more experience is being gained with this drug in the treatment of gonorrhea in the male like with sulfathiazole sulfadiazine resistant cases are encountered not infrequently The most recent studies in gonorrhea seem to show that penicillin is most effective in sulfonamide resistant cases Herrold has found that sulfadiazine may not be effective if the patient has been refractory to 2 or more courses of sulfathiazole In Parsons [4] series every case showed an average decline of the white blood cell count of 2 000 For the renal complications caused by crystallization of the drug in the urine which are most frequent and annoying it is advisable to force fluids to insure a daily output of urine of 1 500 c c and to administer an alkali such as sodium bicarbonate to keep the urinary pH near or above 7 0 In chronic urethritis the results also are good with sulfadiazine

Sulfadiazine is effective also in the treatment of gonorrhea in women and children In a representative series of cases Adair and Hac[5 6] found sulfadiazine to give the most rapid as well as the most satisfactory response in female gonorrhea 98 per cent in 4 days as compared with sulfathiazole 97 per cent and sulfa

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response on an average of a total of 70 0 gm, Finland found 5 which had not responded to sulfathiazole therapy but did respond to sulfadiazine Two cases of chronic gonococcal arthritis showed only fair results

In the treatment of *infections in the urinary tract* sulfadiazine has been found to be effective but no more so than sulfathiazole when administered orally In the test tube using turbidity as the criterion of response Helmholtz[360] compared sulfapyridine sulfathiazole, sulfacetemide and sulfadiazine on *E coli* staphylococci *Aerobacter aerogenes Proteus ammoniae Pseudomonas aeruginosa* and salmonella Excepting perhaps salmonella he felt that in vitro at least sulfathiazole was best sulfadiazine third and sulfapyridine last Clinically, on the other hand, there has been some difference of opinion Creene Pool and Cook[361] from the same clinic studied the results of sulfadiazine in 42 cases of various infections both simple and complicated, and obtained cure in 57 per cent improvement in 29 per cent with 14 per cent failures Previously they had been able to obtain 65 per cent cures in similar cases with sulfathiazole There are others on the other hand who proclaim sulfadiazine as the drug of choice in infections of the urinary tract[36 362] It is generally conceded however that sulfathiazole is to be preferred in staphylococcal infections Infections due to *Streptococcus fecalis* likewise do not respond satisfactorily to sulfadiazine and are best treated with mandelic acid and ammonium chloride or nitrate

When used in treatment of urinary infections parenteral administration seldom is necessary Fluids should be forced as in any treatment of urinary infection, and 2 0 to 3 0 gm (gr 30 to 45) given as an initial dose followed by 1 0 gm (gr 15) every 4 hours Particular caution needs to be exercised if the studies of the patient demonstrate any disturbance of renal function That the drug can be used to good advantage when observed carefully even in the face of latent glomerulonephritis has been shown by Murphy and Wood[16] They treated a case of acute lobar pneumonia with an exacerbation of a latent glomerulonephritis by the usual methods for treating pneumonia with this drug and found that the nephritis was not made worse but improved although it did not heal

As with the other sulfonamide compounds sulfadiazine may not be effective in the presence of calculi retention or deep seated purulent pathology in the urinary tract and so on As outlined in previous sections with this drug too it is essential to study completely the nature and extent of the genitourinary pathology and to employ surgery where indicated in order to obtain the best results with chemotherapy Herrold[363] has advocated the use of sulfathiazole or sulfadiazine in 2 0 gm (gr 30) doses by mouth before and after cystoscopy catheterization and sound passage for the prevention of chills and fever

The sulfonamide compounds have been utilized in ophthalmology chiefly as local applications either as crystals in solution or in ointment form However,

pyridine 93 per cent It seems only fair to point out, however, that in their results the patients on sulfadiazine on the average had a higher blood level, 4 to 6 mgm per 100 c c, than did the patients on the other two drugs where the blood level was 2 to 3 mgm per 100 c c How much difference this might make is purely speculative but with either one of the drugs in the treatment of gonorrhea 5 to 6 mgm per 100 c c is a blood level more in keeping with better results In their use of sulfadiazine to adults they gave 2 0 gm (gr 30) divided into 4 equal doses daily for 6 days They found that children with gonorrhea needed somewhat larger doses to effect a cure and used 0 75 gm (gr 12) per 20 pounds of body weight for 10 days During pregnancy these authors found 12 per cent failures, a rate much higher than in non pregnant patients, which suggested to them that gonorrhea may be more resistant to treatment during pregnancy" This finding may be of interest in the light of Speert s observation [9] that sulfadiazine is ab sorbed poorly from the gastrointestinal tract during labor as discussed under pharmacology of this drug earlier in this section Further, none of the infants in Adair s series developed the infection and none suffered any untoward effects As against a provocative test using silver nitrate in the female Adair and Hac[350] advocate the use of cultures taken on the third or fourth day after a menstrual period as the best provocative test of cure giving the most certain results

There are numerous references to the use of sulfathiazole in the *prophylaxis of gonococcal infections* in both the male and the female with encouraging results These suggest that sulfadiazine also may be effective when used in this way There are however some doubts as to the wisdom of taking small doses of one of the sulfonamides at frequent intervals over a prolonged period of time because of the possibility of the development of sensitivity to the compound If the indi vidual should become sensitive it may make it impossible for the patient to be treated with a sulfonamide should he develop a serious infection or become a battle casualty when his ability to take a sulfonamide might mean saving his life Until more is known about the development of sulfonamide sensitivity it might be well to refrain from using them indiscriminately for the purposes of venereal disease prophylaxis[3 7] The same applies to the possible development by the or ganisms of sulfonamide resistance

Sulfadiazine has proved to be effective also when taken orally in the treatment of *gonococcal conjunctivitis* The method of use recommended by Sweet[3 8] is to give 2 0 to 3 0 gm (gr 30 to 45) as the initial dose followed by 1 0 gm (gr 15) every 4 hours for two weeks In *ophthalmia neonatorum* sulfadiazine has been found to be somewhat less effective and more toxic than sulfathiazole with the same dosage i e 1 gr per pound body weight daily in 6 equal doses for two weeks[354] In *gonococcal arthritis* particularly the acute form sulfadiazine has been found to be very helpful In a series of 16 cases, of which 13 showed a good

intents and purposes remained healed for 3 months under observation after dis continuance of the drug

Sulfadiazine so far has not proved any more promising than sulfanilamide in the treatment of *undulant fever* (brucellosis) [8] Its value has not been estab lished either in the arthritis associated with this disease In a rather unusual collection of 60 cases of *anthrax* Gold found that sulfadiazine was helpful but considerably slower than sulfathiazole or sulfapyridine in causing subsidence of edema It required also larger doses than with sulfathiazole to obtain the desired results When used the drug is helpful when given 3 0 to 4 0 gm (gr 45 to 60) as an initial dose followed by 1 0 to 1 5 gm (gr 15 to 22) every 3 to 4 hours

In the treatment of *typhoid fever* sulfadiazine leaves much to be desired although in some respects it seems to be as good as sulfaguanidine and succinyl sulfathiazole (sulfasuccidine) though they are not satisfactory either In ad ministering sulfadiazine to 40 carriers of *B typhosus* Hardy[369] made quantitative cultural tests of their stools and found a marked initial drop in the organism count suggesting a bacteriostatic effect in the intestinal tract but this benefit did not persist Hence a chronic carrier state was not terminated by this treat ment The drug is also of questionable value in the arthritis that may be asso ciated with typhoid fever

Although sulfaguanidine and succinyl ulfathiazole (sulfasuccidine) have been promoted as intestinal antiseptics there is considerable to be said for sulfadiazine in the treatment of various *dysenteries* In fact some observers have found sulfathiazole and sulfadiazine to be as useful as either of the other two com pounds The disadvantage of both drugs however may be their significant ab sorption and possible sub equent toxicity in given instances which make sulfa guanidine and succinylsulfathiazole (sulfasuccidine) safe in treating intestinal infections The best response has been seen in the Flexner Shiga and Sonne types In outlining the usefulness of chemotherapy in intestinal antisepsis Poth and his co workers have used a shift in the *B coli* count of the feces as an indi cator of sulfonamide efficacy Using such a criterion Rodaniche Kirsner and Palmer found sulfadiazine just as effective as sulfaguanidine and succinylsulfa thiazole (sulfa uccidine) Enterococci and *Streptococcus viridans* were not af fected in the gut by either of the drugs In the treatment of 500 inmates of New York State Institutions for shigella dysentery with sulfadiazine sulfaguanidine and succinylsulfathiazole (sulfasuccidine) Hardy and his associates[3 2] found that sulfadiazine 4 0 gm initially followed by 1 0 gm 3 to 6 times a day, was most effective in curing clinical cases Succinylsulfathiazole was superior however in convalescent and passive carriers of the Sonne type In infants with shigella dysentery likewise[37] sulfadiazine caused a rapid response with good improve ment in 6 to 12 hours and a normal temperature in 48 hours If sulfadiazine is

certain *eye conditions,* including gonorrheal conjunctivitis, non specific conjunctivitis, deep cellulitis and orbital phlegmon, infectious iritis and iridocyclitis, non tuberculous choroiditis, acute suppurative dacryocystitis surgical complications of cataract and glaucoma and perforating and penetrating wounds of the eyeball may be treated quite effectively by oral administration[76] A dose of 2 0 to 3 0 gm (gr 30 to 45) followed by 1 0 gm (gr 15) every 4 hours with a blood level of 5 to 8 mgm per 100 c c usually is adequate Such eye conditions as hemolytic streptococcal staphylococcal, pneumococcal and *B pyocyaneus* infections may require combined local and oral therapy Since the systemic effect of local ocular absorption of sulfadiazine is very slight the added care necessary in other combined local and oral treatment with these drugs is not so essential

As with the other sulfonamide compounds sulfadiazine has been tried in numerous infections and diseases and in some has been found wanting The conditions shown in Table XI make up a considerable list in which either the results have not been good consistently or the drug has been tried in too few cases to formulate final conclusions In some of them other sulfonamide drugs are more effective and satisfactory on the whole than sulfadiazine In these diseases and infections sulfadiazine holds promise of beneficial effects under certain circumstances and therefore, is worthy of further trial

TABLE XI

INFECTIONS AND DISEASES IN WHICH SULFADIAZINE MAY BE OF BENEFIT

Actinomycosis	Staphylococcus
B abortus	arthritis
arthritis	bacteremia
B anthracis	carbuncles
B paratyphosi A B C D	furuncles
B proteus	meningitis
urinary tract infections	osteomyelitis
B pyocyaneus	pneumonia
B tularense	Streptococcus fecalis
B typhosus	Torula
Enteric bacilli Gram negative	Ulcerative colitis
Lupus erythematosus	Virus infections
Malaria (therapeutic)	chancroid
Salmonella	lymphogranuloma venereum
Shigella	trachoma

Finland Peterson and Goodwin[30] report the interesting case of a patient with two large suppurative lesions of *actinomycosis* one of the jaw and the other of the lung and thoracic wall The patient had gone downhill on sulfanilamide and sulfathiazole but improved steadily for 5 months on sulfadiazine He subsequently developed active pulmonary tuberculosis but the actinomycosis to all

TABLE XII

INFECTIONS AND DISEASES IN WHICH SULFADIAZINE IS INEFFECTIVE

Anaerobic streptococci	Sp pallidum
puerperal infections	Strep viridans (oral)
B diphtheriae	Trichina
B tetanus	Virus Infection
B tuberculosis	common cold
arthritis	encephalitis
pulmonary	exanthemata (uncomplicated)
Blastomyces	influenza (uncomplicated)
Chorea	mononucleosis
Enterococci	mumps
Hypertrophic arthritis	pneumonitis
P falciparum	poliomyelitis
P vivax	psittacosis
Rheumatic fever	rabies
Rheumatoid arthritis	smallpox
Rickettsia	Yaws
Rocky Mountain spotted fever	
Typhus fever	

of no use In extensive experiments with 6 compounds in tuberculous guinea pigs sulfadiazine begun 6 weeks after infection was found to be totally ineffective[378] In vitro studies of *Blastomyces dermatitidis* showed that sulfadiazine was ineffective unless used in very high concentrations 150 mgm per 100 c c much too high for clinical consideration[3 9] In *chorea rheumatic fever* and the *atrophic (rheumatoid)* and *hypertrophic types of arthritis* sulfadiazine like the other sulfonamide compounds has been without benefit Boyer s studies have been mentioned already in which sulfadiazine was found to be effective but no more so than sulfanilamide in the prophylaxis of streptococcal sore throats and thus probably useful in avoiding recurrences of rheumatic fever

In the early studies of this drug Finland and his associates reported its use in 14 cases of subacute bacterial endocarditis with one case caused by alpha hemolytic streptococcus apparently cured and one showing temporary improvement No favorable effects of treatment were noted in any of the remaining patients although the drug was tolerated well in most instances over long periods of time during which high blood concentrations were maintained With the extensive interest and great desire for cure that have always been shown with this disease Dick[380] tried heroic measures in a man of 30 to whom he gave 40 gm of sodium sulfadiazine intravenously in 500 c c water Ultimately this patient is reported to have recovered without evidence of permanent injury to the kidney but not until after he had suffered severe cramping abdominal pains vomiting and anuria with blood nitrogen rising to 93 mgm per 100 c c If recovery can be made to follow such heroic measures may well be worth the effort in this disease Dick s

used in the treatment of bacillary dysentery it should be cautioned that not infrequently the patient with acute or chronic diarrhea is dehydrated, and if corrective measures are not carried out promptly, kidney damage is almost certain to follow

Griffits[373] demonstrated an in vitro and in vivo effect in mice of sulfadiazine against *cholera vibrio* and more recently Sadusk and Oswald[374] found sulfadiazine and sulfaguanidine to be about equal, with the former perhaps a little the better

Sulfadiazine may be of benefit in clearing the blood stream of plasmodia in *therapeutic malaria* used in the treatment of syphilis[343] Four to 6 gm a day for a period of 8 to 10 days may be required but even then as many as 25 per cent relapse Occasional benefit has been reported in naturally acquired malaria but on the whole sulfadiazine has not been satisfactory

In *staphylococcal infections* in general the majority of the evidence favors sulfathiazole as the more potent drug Sulfadiazine is quite beneficial, however, and can be used with considerable confidence, if sulfathiazole is not available The new substance, penicillin, promises to be the most potent drug against this stubborn and dangerous organism and eventually may replace the sulfonamide compounds in infections due to this organism if it can be made generally available

Marshall and Teed[375] record the case of a 9 year old white girl with *meningo encephalitis* due to *Torula histolytica* in which sulfadiazine by mouth was effective in bringing about recovery Treatment had to be continued for 60 days with an average blood level of 6 0 mgm per 100 c c

By using 3 0 gm a day in adults and 1 5 gm for children Mills and Mackie[376] felt that sulfadiazine was effective in approximately 50 per cent of cases of *acute* or *chronic ulcerative colitis* They felt that the drug was particularly indicated and especially effective when an upper respiratory infection was a factor in the disease Bargen found[377] sulfathiazole sulfadiazine and sulfaguanidine about equally effective in controlling the infection in ulcerative colitis

In numerous other diseases and infections sulfadiazine likewise has been found to be without effect The list presented in Table XII, on close examination, will be found to be almost identical with the similar list tabulated in the discussion of the other sulfonamide compounds Whether new sulfonamide derivatives will be discovered to be effective against this group of conditions is very questionable What place penicillin or perhaps some other substance will take ultimately in the treatment of this challenging list of diseases in which sulfadiazine is ineffective will be awaited with great interest

With certain anaerobic streptococci, diphtheria and tetanus bacilli sulfadiazine has been found to be without effect In two cases of tuberculous meningitis and one of syphilitic meningitis Finland and his associates[3?0] found it to be

duces very little nausea vomiting cyanosis hepatitis and conjunctivitis and acidosis or a lowering of the plasma CO content does not occur In combining the statistics of the various reactions due to sulfadiazine presented by Finland Plummer, Flippin, Bullowa Spink, Satterthwaite collected by Long Abernathy[4 5] Janeway[4] , Dowling and Lepper[4] the severe renal manifestations occur in from 1 5 to 6 0 per cent of cases Drug rash occurs in 1 0 to 2 0 per cent drug fever in 0 3 to 4 0 per cent Nausea and vomiting has varied from 0 5 to 4 5 per cent leukopenia from 0 9 to 2 9 per cent The figures for acute hemolytic anemia are 0 2 per cent and for agranulocytosis less than 1 0 per cent Thrombocytopenia has occurred in 0 1 per cent in one series (Plummer[11]) leukocytosis in 0 3 per cent in another (Dowling and Lepper [3]) Central nervous system disturbances such as headache dizziness giddiness apathy incoordination nervousness confusion hallucinosis and psychosis have been observed in from 0 1 to 5 0 per cent of cases (Flippin) Some of the more important and interesting ones will be discussed in more detail No reaction peculiar to sulfadiazine has come to our attention Except for the renal complications the incidence of toxic reactions is approximately the same with intravenous sulfadiazine as with oral sulfadiazine

The toxic effects of sulfadiazine on the formed blood elements are variable and usually minimal As with the other sulfonamide compounds a moderate *drop in hemoglobin and red blood cells* with prolonged administration is common and usually without danger Unlike with sulfanilamide *acute hemolytic anemia* with sulfadiazine therapy is quite rare [3] When it occurs it is apt to take place during the first 5 days of treatment The most common reaction of the blood following sulfadiazine therapy is *leukopenia* A slight drop in the white blood cell count occurs quite frequently but that may be due to the benefit of therapy in overcoming the infection However a significant leukopenia may occur in 1 5 to 3 0 per cent of cases and then may develop in one of two ways (a) a gradual depression in the white blood cells to 4 000 or below while the patient is under treatment or occurring in the next few days after therapy has been stopped (b) sudden drop from normal levels to between 3 000 and 4 000 The presence of leukopenia alone when sufficient polymorphonuclear leukocytes (40 to 50 per cent) remain present is no contraindication to the institution or continuation of sulfadiazine therapy when that is indicated The development of agranulocytosis on the other hand demands immediate cessation of drug therapy and active treatment Agranulocytosis is apt to occur only after rather prolonged administration of the drug The blood concentration of sulfadiazine seems to be of little moment in this connection for Rothstein s[4] case of agranulocytosis occurred with a level of 6 5 mgm per 100 c c Curry s case [3] on the other hand had a blood level of 53 9 mgm per 100 c c at the time the neutrophiles disappeared from the blood stream Here again daily white blood cell counts may give

result prompted Hull and his associates[91] to act similarly; they gave 4 cases 30 gm. sodium sulfadiazine intravenously and all 4 patients succumbed. All 4 showed gross hematuria and one patient died with suppression of urine and uremia 11 days after the single intravenous dose. At autopsy a necrotizing nephrosis involving principally the collecting tubules was present[7,1]. Since R. E. Gross[18] made practical the operation of ligation of patent ductus arteriosus, and this congenital lesion is subject to the development of bacterial endarteritis, it is of interest to learn what the sulfonamide drugs have to offer either with the endarteritis alone or in combination with surgery. Dayton and Lindskog[1,3] report the case of a young woman with *Streptococcus viridans* endarteritis superimposed on a patent ductus arteriosus in whom the temperature fell and the general condition improved after three days of sulfadiazine therapy. The blood culture did not become negative, however, until after the surgical ligation. At operation sulfathiazole was applied locally in the wound and sulfadiazine continued 2.0 to 4.0 gm. daily for 3 weeks. The patient recovered. In a more recent comprehensive review of all available cases of patent ductus arteriosus that have been operated upon[4] it appears that the surgical ligation of the ductus alone prevents bacterial endarteritis but not absolutely, and the operation may cure the bacterial infection if it is done immediately after endarteritis develops. It is the opinion of the authors[7,4] that the sulfonamide compounds, fever therapy and transfusions in this situation have only a delaying action at best. The use of full doses of sulfadiazine plus surgical ligation seems to be the best treatment at present.

The virus infections listed are not influenced, per se, by the use of sulfadiazine. If bacterial infection is associated, however, i.e., bacteria susceptible to the action of the drug, sulfadiazine is indicated. It may be of some benefit in such virus infections as chancroid, lymphogranuloma venereum and trachoma, but further studies are necessary to confirm or deny this.

Toxic Effects of Sulfadiazine

When sulfadiazine was first introduced for clinical use it was thought that it produced fewer toxic reactions than either of the other sulfonamide compounds. For certain reactions this continues to be true but not for others, for the toxic effects involving the kidneys are of importance. The chief untoward manifestations involve the kidneys, the skin and a sensitization phenomenon, drug fever. In an extensive study Long[4,7] compared the overall toxicity of the various sulfonamide compounds and found sulfanilamide to produce reactions in 11.9 per cent of cases, sulfapyridine in 15.9 per cent, sulfathiazole in 18.6 per cent and sulfadiazine in 6.5 per cent. Grossly and compared to many of the toxic manifestations that have occurred with other sulfonamides sulfadiazine is less toxic. It pro

duces very little nausea vomiting cyanosis, hepatitis and conjunctivitis and acidosis or a lowering of the plasma CO content does not occur In combining the statistics of the various reactions due to sulfadiazine presented by Finland Plummer, Flippin Bullowa Spink, Satterthwaite collected by Long [7] Abernathy[4] Janeway[4], Dowling and Lepper[4] the severe renal manifestations occur in from 1.5 to 6.0 per cent of cases Drug rash occurs in 1.0 to 2.0 per cent drug fever in 0.3 to 4.0 per cent Nausea and vomiting has varied from 0.5 to 4.5 per cent leukopenia from 0.9 to 2.9 per cent The figures for acute hemolytic anemia are 0.2 per cent and for agranulocytosis less than 1.0 per cent Thrombocytopenia has occurred in 0.1 per cent in one series (Plummer [1]) leukocytosis in 0.3 per cent in another (Dowling and Lepper[43]) Central nervous system disturbances such as headache dizziness giddiness apathy incoordination nervousness confusion hallucinosis and psychosis have been observed in from 0.1 to 5.0 per cent of cases (Flippin[130]) Some of the more important and interesting ones will be discussed in more detail No reaction peculiar to sulfadiazine has come to our attention Except for the renal complications the incidence of toxic reactions is approximately the same with intravenous sulfadiazine as with oral sulfadiazine

The toxic effects of sulfadiazine on the formed blood elements are variable and usually minimal As with the other sulfonamide compounds a moderate *drop in hemoglobin and red blood cells* with prolonged administration is common and usually without danger Unlike with sulfanilamide *acute hemolytic anemia* with sulfadiazine therapy is quite rare [30] When it occurs it is apt to take place during the first 5 days of treatment The most common reaction of the blood following sulfadiazine therapy is *leukopenia* A slight drop in the white blood cell count occurs quite frequently but that may be due to the benefit of therapy in overcoming the infection However a significant leukopenia may occur in 1.5 to 3.0 per cent of cases and then may develop in one of two ways (a) a gradual depression in the white blood cells to 4 000 or below while the patient is under treatment or occurring in the next few days after therapy has been stopped (b) sudden drop from normal levels to between 3 000 and 4 000 The presence of leukopenia alone when sufficient polymorphonuclear leukocytes (40 to 50 per cent) remain present is no contraindication to the institution or continuation of sulfadiazine therapy when that is indicated The development of agranulocytosis on the other hand demands immediate cessation of drug therapy and active treatment Agranulocytosis is apt to occur only after rather prolonged administration of the drug The blood concentration of sulfadiazine seems to be of little moment in this connection for Rothstein's[131] case of agranulocytosis occurred with a level of 6.5 mgm per 100 c c Curry's case[43] on the other hand had a blood level of 53.9 mgm per 100 c c at the time the neutrophiles disappeared from the blood stream Here again daily white blood cell counts may give

no warning of impending danger In connection with a discussion of agranulocytosis and sulfonamide therapy a very interesting observation of Dameshek and Wolfson[431] should be mentioned On the basis that death in agranulocytosis is due to the secondary invasion of bacteria in the absence of leukocytes they[433] gave sulfathiazole along with transfusions, liver extract and pentnucleotide to 2 patients who had developed agranulocytosis from amidopyrine and recovery followed Whether sulfathiazole would be helpful in the treatment of agranulocytosis due to sulfadiazine or whether sulfadiazine could be used beneficially in the therapy of agranulocytosis caused by one of the other sulfonamide compounds is an interesting thought The latter has been reported recently[4]

Marked *leukocytosis* also has been reported to occur after sulfadiazine treatment with white blood cell counts of 57 000 63 000[43] and 90 400[434] The increase occurred chiefly in the mature polymorphonuclear cells and band forms

Kracke and Townsend claim[43] that perhaps the sulfonamide compounds particularly sulfathiazole in their normal action may cause a slight depression of the *blood platelets* They did not obtain a drop in platelet count as such when using sulfathiazole but when the drug was stopped they noted a significant rise in the blood platelet count Corham and his associates[436] report a death due to thrombocytopenic purpura from sulfadiazine Combined with 7 other reported cases due to other sulfonamides the mortality rate was 50 per cent In this instance thrombocytopenia usually precedes the signs of purpura, so that daily or at least frequent observations of the blood platelets on routine blood smears should be helpful in avoiding this catastrophe for the prognosis seems better if the drug can be stopped soon enough

Various manifestations of *central nervous system reaction* to sulfadiazine may occur Perhaps the most common is a minor symptom of excessive nervousness sometimes described by the patient as a jittery feeling Headache mental confusion and giddiness are not uncommon when large doses of the drug are used In elderly individuals as reported by Little[437], more serious toxic effects such as hallucinations numbness of the hands and feet hypesthesia and hyperalgesia may occur In his case the loss of vibratory sense of the ankles and hypesthesia and hyperalgesia in the distribution of the left ulnar nerve persisted Previously it has been stated that upon local application of sulfadiazine to the brain, Hurteau[419] found no significant toxic effects or reactions These findings are somewhat at variance with Pilcher and his co workers[418] who found that sulfadiazine implanted on the brain surface of normal dogs caused them to develop typical attacks of Jacksonian epilepsy Such nervous system effects from systemic application have not occurred

A febrile reaction which is commonly spoken of as *drug fever* is not uncommon during sulfadiazine therapy but less so than has been seen with sulfathiazole

It may occur at any time to complicate the clinical picture and like the leukopenia *may occur even several days after the drug has been stopped* This has been attributed to its slow excretion and is to be feared mostly in patients with poor renal function As with sulfathiazole there may be a slow gradual rise of temperature an erratic elevation or a sharp reaction upward with chill Quite frequently if the patient is questioned closely it will be found that either sulfadiazine or another of the sulfonamide drugs had been taken by the patient previously and had not been tolerated well The previous reaction to a drug may not have been considered significant at the time

A febrile reaction which may occur at any time is seen most commonly after the fourth day of treatment In many instances this fact may be helpful for the *fever of the infection being treated with sulfadiazine often is normal by the third day* If by that time the patient is better and a secondary rise in temperature occurs it may be attributed to the drug Another aid in differential diagnosis *may be the white blood cell count If the white cell count is normal at the time of elevation of the temperature it is likely due to a drug reaction*

Recently Talbot and Adcock[130] have repeated studies with sulfadiazine similar to the studies carried out originally by Lyons and Balberor with sulfathiazole Of 37 patients given a second course of sulfadiazine 6 or 16 2 per cent had fever during the second course 3 or 8 1 per cent reacted to both the first and second courses and 3 or 8 1 per cent reacted to only the second course This incidence is less than comparable studies have shown with sulfathiazole Their studies also bring out that febrile reactions are more likely to occur in patients receiving prolonged courses of treatment with the drug It is also important to *remember that a febrile reaction may be the warning signal of other toxic manifestations* such as skin rashes renal reactions central nervous system toxicity and so on if the drug is not stopped promptly

Repeated courses of sulfadiazine in children also may lead to similar febrile responses during subsequent administration [11]

In connection with this discussion on drug fever it should be pointed out that although sulfadiazine does aid in lowering febrile temperatures it is not a particularly good antipyretic That fact requires emphasis here because altogether too often sulfadiazine is being administered simply because a patient has fever with the excuse that an infection might be present which will respond to the drug *If an antipyretic is indicated salicylates in some form still are preferable*

The most common and perhaps most serious toxic manifestation of sulfadiazine therapy involves the *kidneys and urinary tract* Also it has received the most interest and study For although the original work with this drug suggested a lessened incidence of renal complications because acetylsulfadiazine was more soluble in aqueous solution than the acetyl salts of sulfapyridine or sulfathiazole

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urine alkaline and prevention of excessive blood levels may keep crystallization at a minimum but are no guarantee against it Another factor that has been brought to attention recently is that of temperature From the clinical observa ion that renal complications particularly anuria seemed to occur most commonly when they occurred after a drop in fever and as the temperature was going up again Barnes and Kawaichi[44] studied the solubility of various concentrations of sulfadiazine at different pH values and temperatures As will be brought out in the discussion of the therapy of renal complications increasing the pH of the urine increases many fold the solubility of sulfadiazine and acetylsulfadiazine These authors found that at body temperature with urinary pH 8 0 the solubility of sulfadiazine was 115 whereas at the same urinary pH but at a body tempera ture of 105 the solubility was 170 4 From many such observations in which the factors were made to vary the authors conclude that when a patient has a high fever as in pneumonia he can tolerate a high concentration of sulfadiazine espe cially if the urinary pH is elevated As soon as the temperature begins to drop however the sulfadiazine in the urine has a tendency to crystallize out unless the dose is reduced the fluid intake increased or the urine made more alkaline These various factors will be discussed further under therapy of toxic effects

Microscopic and gross hematuria occur much less frequently than crystalluria in 1 0 to 2 0 per cent of cases taking average doses Previous kidney disease or excessive blood levels of the drug will tend to increase the incidence Renal ten lerness will be found frequently to precede hematuria if it is looked for As with sulfapyridine and sulfathiazole microscopic hematuria does not interdict the use of the drug gross hematuria does In 3 patients with meningitis treated with sulfadiazine by Feldman and his associates loin pain crystalluria and micro scopic hematuria developed but because of the gravity of the disease treatment was continued with careful observation and the symptoms cleared spontaneously and rapidly without complications In fact Louria and Solomon s review of the literature has led them to state that in cases in which recovery has been reported no permanent renal damage has been observed On the other hand serious reac tions can take place without albumin crystals or red cells occurring in the urinary sediment Hence urine examinations of patients on sulfadiazine therapy may not be completely reliable as a criterion of impending reactions or recovery A rather unusual occurrence of interest is the case of a patient reported by Adams[4] in whom a non soluble calcareous radiopaque membrane developed on the epi thelial surface of the renal pelvis which on a roentgenogram gave the appearance of a stag horn calculus Repeated washings of the renal pelvis caused no change Adams advises that operative removal is not indicated for the opaque membrane may slough off and pass spontaneously

Skin rashes occur during sulfadiazine therapy but are much less common than

yet certain untoward effects occur quite frequently The more serious complications fortunately are not common The lesser reactions include crystalluria, microscopic hematuria ureteral colic or pains in the loin or abdomen The more severe reactions are manifested by gross hematuria, oliguria, anuria with increasing nitrogen retention, ureteral calculi and death

Studies of the pathology of the renal lesions have shown that in general there are two types of kidney damage caused by this drug (a) mechanical blockage of the urinary passages and (b) toxic effects on the tubular epithelium[41] Extensive granulomatous inflammation of the kidney may result but this is rather unusual[41] The chief cause of the mechanical irritation is acetylsulfadiazine which makes up the larger part of the urinary precipitate The crystals by mechanical irritation and aggregate formation block the renal glomeruli pelves and ureters and produce chemical inflammation The fact that the harmful urinary crystals are chiefly acetylsulfadiazine seems rather a paradox after the finding that acetylsulfadiazine is more soluble in buffer solutions and normal urine than free sulfadiazine itself[444] Crystallization of free sulfadiazine occurs occasionally Its precipitation is more apt to occur after large doses of sodium sulfadiazine intravenously With the toxic effects on tubular epithelium the glomerular tufts may not be involved and autopsy studies show that sulfonamide crystals are not the cause[364] The mechanism of toxicity in such instances has not been established The microscopic picture of the tubules consists of swelling of some of the epithelial cells flattening of others loss of cells with resulting ulcerations, adhesions over areas of coagulum infiltration of the latter with cellular exudate and extension of the exudate through the tubule into the surrounding interstitium[41] In a fatal case of anuria from sulfadiazine therapy reported by Hellwig and Reed[446] the pathological changes described in the kidneys were likened to the changes that have been observed in bichloride of mercury poisoning

Clinically the most common phenomenon occurring in the urinary tract of a patient being treated with sulfadiazine is crystalluria Crystalluria alone occurs in 30 to 40 per cent of individuals and in itself usually is harmless It may occur at any time in the course of treatment If the urine is allowed to stand the vast majority of patients taking this drug will exhibit crystals in it The crystalluria that is important is that occurring in a freshly voided warm urine Crystallization in the upper urinary tract may result in calculus formation obstruction anuria nitrogen retention and death It has been Dowling and Lepper's[430] observation that with sulfadiazine stone development is not apt to occur unless the blood level was 9 2 mgm per 100 c c or more Ordinarily the amount of the drug given the blood level the duration of therapy the fluid intake and output and the urinary reaction are not the only factors involved in renal complications The sodium salt intravenously increases the crystalluria forcing fluids keeping the

nodosa further clinical observations of this possible association will be awaited with great interest

An interesting interstitial myocarditis following the clinical and experimental use of the sulfonamide drugs has been described [0]

Another very interesting phenomenon is the development of *thyroid hyper plasia* with a state of hypothyroidism caused by the sulfonamide compounds The work of the MacKenzies[1 2] and Astwood and his associates[460] has shown that any one of the presently used sulfonamide compounds causes enlargement of the thyroid gland when administered to rats mice and dogs but does not when admin istered to chicks or guinea pigs Sulfadiazine heads the list followed by sulfa pyridine sulfathiazole sulfaguanidine sulfanilamide and succinylsulfathiazole (sulfasuccidine) decreasing in that order Para aminobenzoic acid or iodine do not prevent it but it is abolished by the administration of thyroid or thyroxin and by hypophysectomy The animals have a low basal metabolic rate and these drugs do not depress further the basal metabolic rate of thyroidectomized rats nor prevent their response to small doses of thyroxin These investigators have felt that the thyroid enlargement is mediated probably through the anterior pituitary the hyperplasia being compensatory to the failure of thyroid hormone synthesis In a discussion of the use of thiouracil in the medical treatment of hyperthyroidism for thiouracil causes the same above changes Williams and Bissell[4 1] give this interesting phenomenon a slightly different interpretation They point out that in rats fed a sulfonamide sulfaguanidine the changes occur ring in the pituitary glands are similar to those following thyroidectomy This suggests to them that the drugs act directly on the thyroid gland inhibiting the production of thyroxin this in turn leading to a decrease in the body metabolism and to an increased activity of the pituitary gland Whether these phenomena occur in human patients has not yet been disclosed

A rather unusual toxic effect has been observed by Satterthwaite[36] in which 2 patients developed stiffness of the neck during sulfadiazine therapy In one case this was sufficient to require lumbar puncture in order to rule out meningitis

Finland Peterson and Goodwin[3] have studied the toxic effects of multiple administrations of the sulfonamides Twenty-one of their cases had received either two or three courses of sulfadiazine and except for occasional microscopic hematuria there were no toxic effects noted Ten of these also had been treated previously with sulfathiazole without toxic reactions Thirty six cases had had other sulfonamide compounds without any toxic effects but when given sulfa diazine there developed reactions in the form of fever rash and urinary symp toms All were mild Fourteen other cases had had other sulfonamide therapy with toxic reactions but when given sulfadiazine none had any untoward effects except transient hematuria All in all the toxic reactions from sulfadiazine in

after sulfapyridine and particularly, after sulfathiazole Though less common they are similar in type to those caused by the other drugs Skin rashes occur in 1 0 to 2 0 per cent of cases and are most apt to take place between the ninth and tenth days of therapy If the rash is a reaction in a subsequent course of treat ment with the drug it will appear sooner in 24 to 36 hours The usual manifesta tion is a simple erythematous or scarlatiniform rash or a maculopapular or mor billiform eruption Nodular manifestations are most unusual although erythema nodosum like lesions have been observed[4] Urticarial and petechial eruptions seem to be rare Purpura with death has occurred[436] Bullous dermatitis[4 3] and severe pemphigus like lesions with exfoliation[454] have been reported

Sulfadiazine appears to be *allergenic* but apparently less so than the other compounds There are no reliable tests to determine sensitization, hence a close watch must be kept for signs of intolerance With a rash usually there is fever of mild to moderate degree and leukocytosis seldom exceeding 15 000, unless the reaction is a severe one Eosinophilia may or may not occur The reaction usu ally will subside within 4 or 5 days after the cessation of sulfadiazine therapy

More recently careful study has shown various toxic manifestations, besides conjunctivitis that involve the *eyes* after sulfonamide therapy, including sulfa diazine A most common ocular symptom when looked for, is myopia[455] In a careful observation of 8 adults, given 4 0 gm sulfadiazine orally in 24 hours, Reynolds and his co workers[4 6] found that ocular muscle balance for near vision and depth perception showed the most marked trend away from normal, but abduction and adduction also seemed somewhat affected In several the blind spot enlarged or the color fields constricted At the end of 36 hours there may be some residual weakness of convergence[4 7] Yellow vision may develop Under ordinary circumstances with treatment of the patient in bed with sulfadiazine such ocular manifestations do not become apparent and probably are of no great moment On the other hand with treatment of ambulatory patients who con tinue at work and in whom visual acuity is important such possible toxic effects should not be lost sight of No evidence of residual damage from large doses or prolonged administration has been described

Several other unusual but highly interesting toxic phenomena to sulfonamide therapy have been described recently that warrant mention The first is the observation of Rich and Gregory[4 8] that with previous serum therapy and/or sulfonamide treatment a sensitization phenomenon may occur involving the blood vascular system manifesting itself as *periarteritis nodosa* According to their clinical observations and experimental work the important factors that may lead to such vascular reactions are the development of sensitization in the patient and prolonged administration of the drug Because of the literally tons of sulfonamide drugs dispensed annually in this country and the high fatality rate of periarteritis

stopped if the contents of the quart measure is at all reddish in color the drug should be stopped If there is any doubt it is wisest to determine the level of blood nitrogen either as blood urea nitrogen or non protein nitrogen For ureteral calculus or anuria the drug must be stopped, and catheterization of the ureters with lavage with warm water or saline or sodium bicarbonate solution may be tried If a catheter cannot be passed up the involved ureter Campbell and Fobes[64] advise ureteropyelostomy with the incision of the kidney pelvis above the obstruction if possible and washing out from above The administration of mercurial compounds as diuretics or the use of magnesium sulfate as a cathartic is contraindicated in such cases

Because of certain chemical characteristics of sulfadiazine and acetylsulfa diazine in the urine there has been much interest in the use of alkalies when giving sulfadiazine to prevent the renal complications The use of alkalies such as sodium bicarbonate was promoted extensively with sulfanilamide in order to prevent acidosis from that drug In the course of time it was learned that was not necessary routinely Then as renal complications developed with the use of sulfapyridine and sulfathiazole alkalies again were tried and often found to be wanting With sulfadiazine this is entirely different Evidence is accumulating to show that the proper use of alkalies has a striking effect in diminishing the renal toxic effects of sulfadiazine

Schwartz and his associates [65] were among the first to recommend alkali therapy for the prevention of sulfadiazine crystalluria in 1941 They gave sodium bicarbonate in amounts equal to the dose of sulfadiazine being administered and noted a decreased incidence of crystalluria Subsequent developments have shown that the amounts they used were not sufficient to give optimum results Jensen and Fox [8] and Gilligan and associates [59] have studied the problem further When the temperature is kept constant 25 C the solubility of sulfadiazine in normal human urine increa es from 16 mgm per 100 c c at pH 5 2 to 1 320 mgm per 100 c c at pH 8 5 At pH 6 0 it is 25 mgm per 100 c c at pH 7 0 110 mgm per 100 c c and at pH 8 0 1 200 mgm per 100 c c [66] As Fox Jensen and Mudge [67] point out increasing the urinary output from 1 000 c c to 2 000 c c a day might as much as double the quantity of sulfadiazine in solution whereas raising the pH of the urine from 6 5 to 7 5 will permit more than a ten fold in crease in solubility To produce such changes in urinary pH may take very large doses of alkalies for the sulfonamides and particularly sulfadiazine are acids and further tend to lower the pH of the urine Accordingly to maintain an alkaline urine it is necessary to administer sufficient alkalies to neutralize the acidity of sulfadiazine in addition to the usual acidity of the urine As shown by Gilligan and associates[4] in further work usually it requires 15 0 to 16 0 gm of bicar bonate daily for an individual receiving 6 0 gm of sulfadiazine orally Twenty

these cases apparently were similar in frequency and in all other respects to those seen in patients who had no previous experience with the other sulfonamide drugs This seemed to be true regardless of whether or not the patient had experienced toxic effects from sulfadiazine Possible sensitivity to multiple drugs is well brought out in a case reported by Nelson[46] of a female with cystitis and urethritis, who was treated and reacted successively to sulfathiazole sulfadiazine, sulfapyridine and sulfanilamide

Treatment of Toxic Effects — The best method of treatment of the toxic effects of sulfadiazine is close observation of the patient with prompt recognition of the earliest signs of toxicity and immediate withdrawal of the drug Little can be done in the way of specific antitoxic therapy except the administration of alkalies in the prevention of renal toxicity to be discussed further on Para aminobenzoic acid has no effect against the untoward reactions of sulfadiazine For mild reactions such as giddiness, nausea crystalluria the forcing of fluids is all that is required while the patient is at bed rest For any of the other reactions the drug should be stopped promptly Fluids should be forced in addition in order to wash out the drug through the kidneys Such a procedure usually will make drug fever disappear very quickly and other reactions will tend to subside rather promptly Fever leukopenia and skin rash may occur or become temporarily aggravated even after the drug has been stopped and the blood level is falling For severe anemia or granulopenia blood transfusions liver therapy and pentnucleotide may be required Erskine[463] has attempted desensitization in a few cases of skin rash by the following procedure If the condition for which the drug is being given is fully under control when the rash develops usually on the 8th day in his experience he stops the drug If more drug is needed he drops the dosage to half or gives perhaps 0 25 to 0 5 gm (gr $3\frac{3}{4}$ to $7\frac{1}{2}$) every 8 hours for 24 to 48 hours with the addition of an alkaline diuretic This procedure he believes tends to desensitize the patient for future use of the drug If, as happens occasionally a rash appears after sulfonamide treatment has been stopped he uses 0 25 gm (gr $3\frac{3}{4}$) three times a day for 3 days even if no drug is indicated for the disease Likewise he believes this has a similar effect

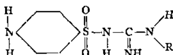
For minimal crystalluria or microscopic hematuria treatment need not be instituted Careful observation for more prominent symptoms and signs is all that is required For pronounced crystalluria gross hematuria severe loin pain or the development of oliguria the drug should be stopped A useful procedure, particularly in the home is to have all the voided urine collected in a quart measure so that it can be inspected daily On the average dosage of sulfadiazine the fluid intake should be between 2 000 and 3 000 c c daily to insure a daily urinary output of 1,000 to 1 500 c c If the quart container is at least not filled after 24 hours, fluids should be increased or the drug dosage diminished or

PART VI

Sulfaguanidine (Sulfanilylguanidine)

Introduction

Since the beginning of sulfonamide chemotherapy chemists the world over have been attempting to develop derivatives and new related compounds for more effective and less toxic chemotherapy in the treatment of disease In an extensive study of cyanamide derivatives Roblin and his associates[470] synthesized sulfanilyl guanidine in 1940 Guanidine is one of a large group of compounds which may be prepared from cyanamide The formula may be any one of four because these substances are potentially tautomeric isomers According to later studies on sulfanilylguanidine the alkali solubility properties seem to favor the following formula



Given the non proprietary name of sulfaguanidine it has been accepted by the Council of Pharmacy and Chemistry for the treatment of certain intestinal dis orders Shortly after Roblin s work Marshall and his co workers[471] independ ently reported this compound Their approach to the subject introduced a new feature in the use of these drugs Inasmuch as the sulfonamide compounds are so effective in the eradication of organisms from the urinary tract it was rea soned that in infections confined to the intestinal tract it would be highly desir able if an active compound could be found which was both fairly water soluble and at the same time poorly absorbed Sulfaguanidine seemed at first to satisfy these requirements Sulfaguanidine is soluble in water at body temperature to the extent of a little over 200 mgm per 100 c c (0 2 per cent) This is greater than the solubility of sulfapyridine sulfathiazole or sulfadiazine but much less than that of sulfanilamide Further in its chemistry in contradistinction to the other sulfonamide compounds sulfaguanidine is not soluble to any extent in alkali hence a soluble sodium salt cannot be prepared It is too weak an acid to be meas ured in aqueous solution

Pharmacology of Sulfaguanidine

In its pharmacological properties sulfaguanidine is absorbed from the intes tinal tract fairly rapidly An interesting paradox is the fact that it is absorbed

four gm divided into 6 equal doses may be used for short periods without altering the carbon dioxide combining power of the plasma or causing ill effects The important thing is to give sufficient quantity of alkali at 4 hour intervals day and night to maintain the urine pH at 7 0 or above They[498] advise continuation of alkali therapy for one day following cessation of sulfadiazine administration Even in the presence of urea splitting organisms, where the urine may be strongly alkaline adjuvant bicarbonate therapy is indicated in order to maintain the appropriate pH in the urine in the tubules In cardiac or renal insufficiency with edema, where sodium may be contraindicated, great care must be used or a potassium salt substituted Adjuvant alkali therapy is indicated, particularly when sodium sulfadiazine is given intravenously

Another interesting approach to the production of increased solubility of sulfadiazine has been through the use of urea Sobin and his associates[499] observed that in vitro the solubility of acetylsulfathiazole increased at a given pH in proportion to the specific gravity of the urine Studies suggested a relationship to the presence of urea and the administration of urea to rats prevented urinary precipitation of both sulfapyridine and sulfathiazole According to their studies the urea effect could not be attributed to diuresis but seemed to depend upon a solvent effect on both the free and acetylated sulfonamide compounds This principle does not seem to be so applicable to human patients for in another type of experiment that the writer performed giving large doses of urea with sulfathiazole or with sulfadiazine, crystals of the sulfonamide drugs were seen occasionally In the clinical application, moreover, sodium bicarbonate would be much easier to use and less distasteful

March 1 1944

from the small bowel and that which is absorbed is excreted very rapidly by the kidneys with a resultant low blood level

When given to human patients in therapeutic doses blood levels of 1 0 to 4 0 mgm per 100 c c may be obtained while at the same time a concentration of 200 to 1 000 mgm per 100 c c may exist throughout the entire length of the intestinal tract An obstructive lesion in the intestinal tract delaying movement of the drug through the gut makes for greater absorption and higher blood levels Probably the presence of ulcerative lesions and denuded surfaces also allows for increased absorption into the blood stream The amount that is absorbed usually diffuses quite readily throughout the body except into the spinal fluid The determination of the drug in blood urine body fluids and tissues is by the method used for sulfanilamide

In general it may be stated that in the human patient sulfaguanidine therapy produces either a marked decline in the total count of bacterial flora of the feces or a transformation from a predominance of gram negative bacilli usually coli forms to a predominance of gram positive elements usually streptococci Both changes may occur A remarkable similarity in this respect was noted by Rodaniche Kirsner and Palmer in patients tested with all four sulfonamide compounds sulfapyridine sulfathiazole sulfadiazine and sulfaguanidine With the latter drug however there was a somewhat greater response The reduction of coliform bacilli in some cases furthermore appears to retard the synthesis and absorption of vitamin K in the intestine

Sulfaguanidine appears to be conjugated to a considerable extent somewhat more than sulfapyridine but the conjugated form of sulfaguanidine is more soluble both in water and in urine than that of sulfapyridine In some instances it appears also that within limits the higher the blood concentration the greater the degree of acetylation It is acetylated in the mouse rabbit monkey and man but not in the dog The greater solubility of the acetyl salt favors a lessened tendency to precipitation in the kidneys It is excreted readily in the urine approximately 30 per cent occurring in the conjugated form Renal clearance determinations of sulfaguanidine in the dog show that it is excreted about three times as rapidly as sulfanilamide If the blood levels become high enough with rapid excretion crystallization of this compound occurs also in the urine

When sulfaguanidine is implanted locally into the peritoneal cavity it produces a response with absorption similar to that elicited by sulfathiazole When put in the peritoneal cavity in dogs Throckmorton[4] found little evidence of serosal damage or attachment that it disappeared grossly from the peritoneal surface in 3 to 5 days and that the cellular response was comparable to sulfadiazine About 30 per cent of the animals exhibited splenic changes with dark spleens which he attributed to the possible formation of sulfhemoglobin When

to a larger extent, when very small doses are given, but to a very small extent, when large doses are used, if measured in terms of blood levels of the drug[49]. The total amount of the drug absorbed from the intestine seems to depend more on the time interval between doses than upon the actual size of the dose. Also when the same total dose of drug is divided into several equal portions and given at three hourly intervals in contradistinction to administration as a single dose the maximum blood concentration may be doubled. The explanation of this probably is that absorption occurs mainly in the small as opposed to the large bowel. For in man it has been found that one or two large doses per day will produce a much lower maximum blood concentration than the same total daily dose divided into several portions and given at frequent intervals. Moreover saturation of the intestinal contents as well as the total amount of drug absorbed appears to depend also upon the rate of passage of the contents along the intestinal tract as judged by the number of stools per day[45]. Hence a patient having numerous stools per day can tolerate the drug better than one with few stools, for less will be absorbed.

To demonstrate further that sulfaguanidine is absorbed little or not at all from the large bowel Keeley and McCord[483] introduced the drug into the proximal and distal loops of colostomies of 5 patients. After 6 hours blood levels of the drug were zero indicating that sulfaguanidine is not absorbed from the left half of the colon in human beings. In a careful study of the feces of 5 subjects given 3.0 gm. after breakfast followed by 1.0 gm. at noon, 1.0 gm. that evening and 1.0 gm. the next morning Hawking[484] found 495 mgm. of the drug per 100 gm. feces present at the end of 12 hours, 700 mgm. in 17 hours and 2,500 to 3,900 mgm. in 24 to 36 hours. This is a much higher concentration of fecal excretion than he found in comparable studies with sulfapyridine, sulfathiazole and sulfadiazine.

Since it has been found that the excretion of sulfaguanidine in the urine is reallv verv rapid[49], Ambrose and Haag[486] proposed the idea that the low blood levels of the drug may not necessarily mean poor absorption but rather very rapid excretion of that which is absorbed. Good absorption and very rapid excretion in the urine, however, will not account for the high concentrations that are recovered in the feces. On the assumption that good absorption with reexcretion into the intestinal tract by way of the bile or through the intestinal walls may account for the high fecal drug content Hawking[487] gave sulfaguanidine subcutaneously to cats and on death found much of the compound still visible at the site of implantation. His figures provide evidence that sulfaguanidine which has been absorbed is excreted almost entirely into the urine, and that the amount, which passes from the blood into the bile or into the lumen of the intestines is negligible.

The present concept is that a significant amount of sulfaguanidine is absorbed

initially followed by 0 05 gm per kilo every 4 hours On an average an initial dose of 4 0 to 6 0 gm (gr 60 to 90) followed by 3 0 gm (gr 45) every 4 hours has been quite satisfactory giving a blood level less than 2 0 mgm per 100 c c With severe diarrhea however more frequent and larger doses may have to be given When the number of stools has been reduced to 5 or less per day the maintenance dose should be reduced to 3 0 to 4 0 gm (gr 45 to 60) every 8 hours In the absence of diarrhea one or two doses a day may be sufficient to keep the contents of the large intestine saturated with the drug In adults the weight of the patient can be disregarded safely and a maintenance dose of 3 0 to 4 0 gm given at the desired intervals The dose for children is essentially the same as that for adults The drug has even been used for the treatment of gastroenteritis of premature infants in doses of 0 5 gm (gr 7½) initially followed by 0 25 gm (gr 3¾) every 3 hours with satisfactory response[9] Prolonged use of the drug should be avoided since certain essential growth factors such as biotin are synthesized to a considerable extent by the bacteria of the bowel

Toomey has advised the supplementary administration of vitamins B and K *when sulfaguanidine is used for a long period of time*[3] *Bargen s method*[3] has been to give the sulfaguanidine at four hour intervals for two weeks with repetition of the course after a rest period of one week provided untoward results have not occurred

In studies in mice in which the blood concentrations were the same Marshall found that sulfaguanidine was slightly less active than sulfanilamide against a streptococcus infection and as active as sulfapyridine against a pneumococcus infection In the intestinal tract however sulfaguanidine has little effect on streptococci In vitro sulfaguanidine and sulfanilamide were equally effective against *E coli* and the Newcastle and Flexner strains of dysentery bacilli Sulfanilamide however seemed slightly more effective in vitro against *E typhi* and the Shiga and Sonne strains of dysentery bacilli Further in mice sulfaguanidine seems to reduce the concentration of lactose fermenting bacteria chiefly of the coliform group in the intestine and has been found to be effective also against *E cholerae suis* and to some degree against *S parathyphi A* but ineffective against other organisms of the salmonella group[1 4]

Since diseases localized mainly or entirely in the intestinal tract cannot be produced satisfactorily in animals direct experimental assessment of the therapeutic value of the drug has not been obtained Most of its evaluation has been from its clinical application to human patients In Table XIII are listed the various organisms and conditions against which sulfaguanidine has been used Because of the limited use to which sulfaguanidine can be put the number and variety have not been very great hence they have been condensed into a single table Some of the results have been quite variable

placed in the pleural cavity likewise it is absorbed about the same as sulfathiazole with only a moderate reaction resulting[4]

There are two additional effects produced by sulfaguanidine in vivo that are unusually interesting and merit special mention Perhaps they might be considered in the discussion of the toxic effects of this drug for they are the catabolic results of the drug on body economy However, they have not been described with the use of the drug in human patients The two metabolic effects are inhibition of growth and disturbances of the thyroid gland

When young rats are placed upon a synthetic ration, sulfaguanidine presumably by preventing or decreasing the synthesis of essential nutrients by the intestinal flora reduces the rate of growth This effect is accompanied by a state of hypoprothrombinemia Vitamin K counteracts the prothrombin effect only, whereas p aminobenzoic acid and a liver extract factor counteract both the effects[490]

The effect on the thyroid gland is not limited to sulfaguanidine, for the other sulfonamide compounds act similarly MacKenzie and MacKenzie[49] noted that, when sulfaguanidine was administered to rats particularly but also to mice and dogs, it produced an enlargement of the thyroid gland with a resulting low basal metabolic rate This effect does not occur in chicks or guinea pigs It is prevented by thyroxin administration or by hypophysectomy but not by p aminobenzoic acid or iodine If rats have been thyroidectomized previously, the administration of sulfaguanidine does not depress further the basal metabolic rate, and it does not prevent the animal s response to small doses of thyroxin According to Astwood and his associates[46] the thyroid hyperplasia is considered to be compensatory to the failure of thyroid hormone synthesis Further studies of these phenomena may prove of considerable interest in connection with these drugs as they are particularly suggestive of nutritional deficiency

Clinical Uses of Sulfaguanidine

Sulfaguanidine has been used in the treatment of certain infections of the gastrointestinal tract and in an attempt to sterilize somewhat the colon before operative procedures upon it Its effect is predominantly a local one upon the intestinal flora and not a systemic action For this reason parenteral administration is of no use For infections in the intestinal tract the drug is to be given by mouth It is supplied in tablets of 0 5 gm (gr 7½) for oral use and as a powder It may be given suspended in water or milk Large doses are to be used in order to avoid high blood levels and at the same time to saturate the bowel with the drug in solution which then can be effective wherever it comes into contact with the mucosa The recommended dosage is 0 05 gm (gr ¾) per kilo

resisted all other treatment, these authors observed by sigmoidoscopy rapid healing of ulcers They advise that Shiga antitoxin need not be administered along with sulfaguanidine except in fulminating or severely toxic cases of Shiga dysentery Most of their cases were mild and did not require serum Brewer, however gave 30 000 units of anti serum to his patients with shigellosis along with sulfaguanidine

In an interesting endemic fortunate for its control value at the Norwich State Hospital Opper and Hale [1] were able to give the drug rather critical evaluation In 1939–1940 they encountered 38 cases of Flexner dysentery of which 18 had the disease in an active form and 20 were carriers On symptomatic treatment recovery occurred but 57 per cent retained the organisms in the intestinal tract longer than one month In 1941–1942 a similar outbreak occurred in 33 cases with the same organism with 15 presenting diarrhea and 18 as carriers On a dose of sulfaguanidine of 4 0 gm (gr 60) daily for one week all but 4 responded to the drug and those 4 responded to a second course

Lyon who has had considerable experience with this drug has found that when there is blood and pus in the stools and when fever is present the results with sulfaguanidine treatment are nearly always satisfactory When the dysentery bacilli have disappeared from the stools however and there is no more blood or pus present i e when the stage of bacterial activity has passed and the stool is of the green watery type sulfaguanidine seems to have a less beneficial effect Lyon believes also that there is reason to institute a moderately restricted high protein diet in order to obtain the best results of treatment He advises the use of cultured lactic acid milk cottage cheese custards and vitamins

From an extensive experience in tropical diseases Manson Bahr advises several useful supplementary measures in conjunction with sulfaguanidine in the treatment of bacillary dysentery Bahr uses 6 to 9 gm of the drug daily for the first five days with sedative purgatives a nutritious soft diet excluding milk but including arrowroot and blood transfusions He advises antidysenteric serum in severe cases and intestinal irrigations with eusol (calcium hypochlorite and boric acid) in chronic cases For sedation morphine or tincture of opium seems best Large doses of salts preferably sodium sulphate 4 0 gm (ʒ 1) every 3 hours for the first 48 hours then 4 times a day until the stools become feculent give a satisfactory purgative effect The patient is not to be starved Milk should be avoided but fluids should be given freely 4 to 6 pints daily of lemonade or barley water to counteract dehydration The diet should consist chiefly of junket jellies beef tea chicken broth ice cream and arrowroot If the patient is very ill it is advisable according to Bahr to give antiserum 80 c c intramuscularly or 50 to 60 c c intravenously Antiserum should not be given subcutaneously

For the *carrier state* or for *prophylaxis* in bacillary dysentery sulfaguanidine

TABLE XIII

ORGANISMS AND DISEASES AGAINST WHICH SULFAGUANIDINE HAS BEEN USED *

Effective	*Doubtful Effect*	*Ineffective*
Br abortus	diarrhea simple	Cholera vibrio
Dysentery	diverticulitis	E paratyphi B
Flexner bacillus	F typhi	Entameba histolytica
Newcastle bacillus	lymphopathia venereum	
Shiga bacillus	regional ileocolitis	
E coli	Sonne bacillus	
	ulcerative colitis	

* Words in italics are those conditions in which sulfaguanidine is especially effective

In vitro in high concentrations sulfaguanidine has been reported to have an inhibiting effect on *Br abortus*[495] Sarvis[496] has treated three patients with brucellosis with this drug in whom he claims recovery The very chronicity of this disease will make further similar observations desirable

It has been in the treatment of *bacillary dysentery* that sulfaguanidine has been found most useful According to Manson Bahr[497] in the medical history of the World War of 1914–1918 bacillary dysentery took second place in importance among war diseases Of every 100 people affected about 20 became carriers for several months, thereby acting as the starting point of fresh epidemics In the present global conflict, in which troops are widely scattered diarrhea is again a very prominent feature, and sulfaguanidine is being used with considerable success It is being found that sulfaguanidine appears to be effective against all of the various strains of dysentery bacilli It seems, however, to have its most striking effect in the treatment of the toxic *Flexner* and *Shiga* strains There are numerous reports chiefly of cases of Flexner bacillary dysentery, in which the results have been quite striking In one large series of 300 cases reported by Lyon[498], using the dosage outlined above the over all results were good but best when treatment was begun early When the treatment was begun in the first five days of the illness recovery usually occurred in [illegible] to 5 days When employed later the results were consistently good, sometimes amazing but failures were encountered somewhat more frequently The results were less good, if therapy was started after the disease had existed 11 days or longer Brewer[499] on the other hand obtained just as good results in chronic as in acute cases with 77 per cent cure in the former and 73 per cent in the latter His cases included both the Flexner and Shiga types In another large series of 500 cases in the Middle East of which many were of the Shiga type Fairley and Boyd found sulfaguanidine a specific cure It appeared to them to exert a bacteriostatic or bactericidal action which led rapidly to decrease in toxemia and to cessation of damage to the intestine In subacute and long standing chronic cases that had

resisted all other treatment these authors observed by sigmoidoscopy rapid healing of ulcers They advise that Shiga antitoxin need not be administered along with sulfaguanidine except in fulminating or severely toxic cases of Shiga dysentery Most of their cases were mild and did not require serum Brewer, however gave 30 000 units of anti serum to his patients with shigellosis along with sulfaguanidine

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For the *carrier state* or for *prophylaxis* in bacillary dysentery sulfaguanidine

may be quite effective It is a drug that is safe enough to use in ambulatory or home patients In an outbreak, such as reported by Scott , it may quickly bring the disease under control as well as being an effective prophylactic when given to those exposed A prophylactic dose, when diarrhea is not present, should consist of 3 or 4 of the 0 5 gm (gr 7½) tablets daily This dose may be used in children as well as in adults

There is evidence somewhat limited, to suggest that sulfaguanidine is some what less effective against the clinically less toxic *Sonne* strain of dysentery bacillus one which so frequently gives rise to mild, afebrile diarrhea without blood and often with little pus in the stools Its very successful use has been reported however The dosage is the same as that for the Flexner and Shiga types

In the treatment of acute bacillary dysentery in infants and children sulfa guanidine has caused prompt subsidence of symptoms In children particularly Lyon [3] has stressed the importance of water and chemical balance if treatment is not begun until several days have elapsed As he aptly points out, sulfaguani dine does not take the place of proper fluid intake, glucose saline, calcium, blood serum or whole blood transfusions , when these have been depleted

In various *non specific diarrheas* in either children or adults sulfaguanidine may or may not be helpful Some investigators are of the opinion that in any severe bloody or purulent febrile diarrhea, the drug should be given therapeutic trial Such a trial should consist of the regular dosage for 3 to 5 days, to be stopped if there is no response In such cases sulfathiazole and even sulfapyridine have been found to be beneficial With either of those two drugs an initial dose of 4 0 gm (gr 60) with 1 0 gm (gr 15) every 4 hours usually is sufficient Under certain circumstances such as vomiting or unconsciousness sulfathiazole has the added advantage that it can be given parenterally, whereas sulfaguanidine has not been developed for such use On the other hand Fairley and Boyd [o] condemn strongly the use of sulfapyridine or sulfathiazole in dysentery, since the patients are so often dehydrated and ' kidney damage is almost inevitable '

In cases of simple watery diarrhea without significant bacterial infection or without blood or pus in the stools in which adequate chemotherapy with sulfa guanidine or sulfathiazole had failed Lyon[19] attempted to analyze the causes of failure He felt they were either (a) previously undetected acute bacillary dysentery with the subsequent development of a post infection, intestinal indi gestion with a green watery stool, (b) a parenteral infection not discovered or (c) diarrhea due to local or systemic virus infection which do not respond to sulfonamide chemotherapy

Attacks of *diverticulitis* may be shortened somewhat by the administration of 2 0 to 3 0 gm of sulfaguanidine every 4 to 6 hours It is best used with the diarrhea and not with obstruction caused by an inflammatory mass

Sulfaguanidine has been uniformly disappointing in the treatment of *chronic non specific ulcerative colitis* Mills and Mackie [4] felt that it gave some improvement in 82 per cent of the cases in which it was used when given for a long time It seemed of no benefit when the diarrhea was severe or in fulminating cases With the presence of ulcerations in the bowel there may be considerable absorption of the drug with resulting toxic reactions Kirsner and associates [95] study of 12 cases showed that a usual dosage of 10 to 15 gm daily frequently gave blood levels of 10 mgm per 100 c c of the drug In what Bargen calls ulcerative colitis occurring in the late stage of bacillary dysentery he has claimed benefits with sulfaguanidine when given in doses of 1 0 gm (gr 15) every 2 hours or 2 0 gm (gr 30) every 4 hours to a total of 12 0 gm in 24 hours He gives the drug daily for two weeks allows the patient to rest a week, then repeats a second course for two weeks [77]

In the ulcerative colitis caused by *lymphogranuloma venereum* sulfaguanidine may be of benefit but does not appear strikingly better than the other sulfonamide compounds When given over a period of several months 10 0 gm daily it has been found to decrease the number of rectal discharges and the amount of bleeding There may be improvement as evidenced further by involution of boggy edema and relief of congestion of rectal and perirectal tissues[5, 6] A number of observers have reported an added feeling of well being that sulfaguanidine treatment gives to these patients *Regional ileocolitis* may be benefited temporarily by the drug

Sulfaguanidine for the treatment of *typhoid fever* was received hopefully The results have been quite variable perhaps slightly better in eradicating the carrier state than in the treatment of the active disease There are reported [7] isolated instances of good results but there are just as many unfavorable results on record [4, 9] In a controlled series studied by Hall [1] the drug was used in 20 patients with proved typhoid fever while a similar number of proved cases in the same ho pital at the same time receiving no drug served as controls In this study the drug was of no value in the treatment of typhoid fever There may be some clearing of the sensorium and the appetite may improve and the number of typhoid organisms in the stools may be decrea ed but there is no good evidence that the drug has any particular influence on the ultimate course of the disease

Both encouraging and discouraging results have been reported in the use of sulfaguanidine in the treatment of the *carrier state of E typhi* Hoagland has *reviewed this subject and with good results in 2 cases reported by him he suggests* that previous failures may have been due to too small dosage of the drug Whereas previous authors had attempted treatment by the use of 10 0 to 12 0 gm daily Hoagland used 4 0 gm (gr 60) 5 times a day or a total of 20 0 gm daily He therefore believes that sulfaguanidine should be tr ed in the treat

ment of the typhoid carrier state with doses as high as 20 0 gm daily, if smaller doses are ineffectual In large series of cases given the drug in the usual manner or in small doses, there has been no effect on the bacillary excretion in the stool

In *E paratyphi* infections sulfaguanidine seems to be of little or no use Lyon[503] feels that perhaps as many as a third of patients with these infections may be benefited Scott Beeson and Hawley[91] gave the drug to 58 patients with paratyphoid B infections and found it ineffective in doses of 0 1 to 0 2 gm per kilo daily for 10 days They divided their cases into three groups (a) acute stage (b) early convalescent stage and (c) patients excreting organisms after several months In none of them was there evidence that the drug had any effect In fact there was no difference between the treated and untreated cases

In vitro sulfaguanidine exerts some effect on *V cholerae* but less than sulfathiazole or sulfadiazine[374] In a rather large series of 218 cases of cholera reported by Chopra and his co workers[513] sulfaguanidine in an initial dose of 1 0 gm (gr 15) followed by 0 5 gm (gr 7½) every 6 hours for 72 hours was felt to lower the mortality rate of 6 38 in 94 control cases to 3 21 The patients on sulfaguanidine therapy passed fewer stools per day and required also less intravenous saline Intravenous saline solution so helpful in the treatment of the dehydration of cholera did not seem to aid in the chemotherapy in this series In a more recent study of cholera in which 50 patients received the drug and 88 did not sulfaguanidine was found to be without appreciable effect[514] Many more studies of this disease are necessary however before the drug can be recommended or discarded

Sulfaguanidine has been of no value in the treatment of *amebic dysentery*

Firor and Jonas [15] introduced the *pre operative use* of sulfaguanidine in the preparation of 12 patients who needed operations upon the colon This use of the drug is for the purpose of attempting to rid the colon of as many bacteria as possible in order to avoid post operative infections Although their attitude was conservative the authors felt optimistic and stated that perhaps two of the patients would have died except for the use of this drug Firor and Poth s [16] subsequent experience has modified this attitude Previous discussion has brought out that sulfaguanidine will reduce markedly the number of *E Coli* in the intestinal tract but *many other organisms remain uninfluenced* It does not sterilize the intestinal tract Spink and Wangensteen[1] used the drug in 20 patients who were to undergo colonic resections but were unable to draw any conclusions as to its prophylactic value Because of the frequent difficulty of oral medication post operatively its usefulness may be limited after operation Further it should be remembered that in depressing the coliform bacteria in the bowel sulfaguanidine may interfere with the synthesis and absorption of vitamin K by some patients According to Marshall[46] it now appears that the use of a sulfonamide

locally in the abdominal cavity and systemically at the time of operation may prove more valuable than an attempt to reduce the bacterial flora of the colon with sulfaguanidine before operation For intraperitoneal implantation sulfanilamide is perhaps best and for systemic effect sulfadiazine orally or parenterally as conditions warrant is at present the drug of choice

An interesting observation on the use of sulfaguanidine is that of Pinkston and Burch [17] In 20 cases of *mycotic infections* of the vagina they report the cure of 9 instances by washing the vagina with green soap and water drying then applying 3 0 gm of the powdered drug either by insufflation or in capsule The cultures rapidly became negative Because of its relatively high solubility sulfaguanidine may have some place in the treatment of infections by *local application* Other results of such use of the drug however have not been reported

Toxic Effects of Sulfaguanidine (Sulfanilylguanidine)

Because that amount of sulfaguanidine which is absorbed from the gastrointestinal tract is very rapidly excreted by the kidneys with resulting low blood concentration the acute toxicity of sulfaguanidine for comparison with the other drugs has been somewhat difficult to determine after oral administration Its toxic effects differ considerably in the different species of animals tested and vary from those which have been seen in human patients

Experimentally under the same conditions [51] sulfaguanidine is about as toxic as sulfathiazole In the rabbit Corwin[5] has found the drug to be rapidly fatal They die with renal splenic and hepatic lesions Sulfaguanidine crystals appeared in the renal tubules pelves ureters and bladder There was a reduction in the size of the spleen with atrophy of the Malpighian bodies and pulp Similar lesions could not be produced in dogs or monkeys and have not been observed in human patients The explanation may be that dogs monkeys and humans do not acetylate the drug as highly as the rabbit The dog often can tolerate enormous doses such as 5 0 gm per kilogram body weight for as long as 50 days[514]

The effect of sulfaguanidine on rats has been spoken of already It reduces the rate of growth of young rats and causes a hyperplasia of the thyroid gland In addition Daft and his associates [19] have observed extensive hyaline sclerosis and calcification of blood vessels in rats fed this drug particularly in the small arteries of the heart lungs kidneys pancreas and submucosa of the gastrointestinal tract They found also instances of leukopenia agranulocytosis bone marrow aplasia occasional anemia and a dermatitis which could be prevented or treated with biotin Succinylsulfathiazole (sulfasuccidine) has been found to produce also much the same changes in rats Whether these changes are the result of some dietary deficiency produced by sulfaguanidine or whether due directly

to the drug or some compound derived from it, the authors were unable to state That such pathological changes may be the result of secondary nutritional disturbances is suggested by the recent studies of Welch and Wright [1] using succinyl sulfathiazole (sulfasuccidine), which is in many ways a comparable drug

From the reports in the literature on the use of the drug in human patients the over all toxicity of sulfaguanidine averages about 1 to 2 per cent The toxic reactions that have been observed are essentially the same as those seen with the other sulfonamide compounds They include chiefly headache nausea, vomiting skin rashes, fever conjunctivitis, occasional hemolytic anemia and microscopic hematuria Untoward effects seem slightly more frequent with this drug than with succinylsulfathiazole (sulfasuccidine) perhaps because the former is more readily absorbed Headache pyrexia skin rash and conjunctivitis appear to be the more common reactions In his treatment of bacillary dysentery West [1] has noticed a high percentage of constipation severe in 15 per cent of patients given sulfaguanidine It was of moderate degree in many others Smyth and associates record the cases of 2 humans being treated for Flexner dysentery who showed sensitization phenomena upon the second administration of a course of sulfaguanidine Anderson and Cruickshank[5 3] found that crystalline deposits occur in the urine when the concentration of the drug is over 175 mgm per 100 c c of urine Hence it is important with this drug also to maintain an adequate fluid intake and output in order to avoid local toxicity or irritation in the urinary tract When sulfaguanidine crystals appear in the urine they may be identified under the microscope without resorting to chemical analysis as simple rectangular oblong plates with slight bulging in the long axis They may vary markedly in size however being glass clear or having a fine mesh like pattern Occasionally they tend to conglomerate, forming crosses or star like structures[311] Blood level of the drug may be no accurate guide for toxic effects as Cole s[5 4] case developed oliguria with a blood level of 2 0 mgm per 100 c c Prompt withdrawal of the drug and forcing of fluids brought about a rapid recovery

The treatment of the toxic effects of sulfaguanidine is essentially the same as that for the other sulfonamide compounds, namely prompt withdrawal of the drug and the forcing of fluids In addition it is useful to give repeated enemata to help eliminate the drug from the body Whether adjuvant alkali therapy is useful in preventing crystalluria with this drug has not yet received extensive trial As with the other compounds no specific substances or drugs have been found which are contraindicated during sulfaguanidine therapy

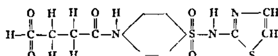
March 1 1944

PART VI-A

SUCCINYLSULFATHIAZOLE (SULFASUCCIDINE)

Introduction

This new compound is one of a series of N^4 dicarboxylic acid substituted sulfonamides introduced by Poth and Knotts in 1941 for intestinal antisepsis [5] It has been synthesized by Moore and Miller and it occurs as a white practically odorless and tasteless crystalline powder soluble in water at 37 C to the extent of about 70 mgm per 100 c c It is sparingly soluble in alcohol and acetone insoluble in chloroform ether and benzene It melts with decomposition at 192 to 195 C Its molecular weight is 373 4 Succinylsulfathiazole 2 (N^4 succinyl sulfanilamido) thiazole monohydrate 2 (p succinylamino benzene sulfonamido thiazole monohydrate) has the formula $C_{13}H_{13}N_3O S H O$ with the following structure



It has been accepted by the Council of Pharmacy and Chemistry as succinyl sulfathiazole [7] It has been placed on the open market as sulfasuccidine including the trade name sulfasuxidine It may be obtained as a powder or in tablet form 0 5 gm (gr 7½)

The drug is a strong acid and dissolves in an aqueous solution of sodium bicarbonate with effervescence to form the soluble sodium salt The sodium salt of succinylsulfathiazole however has a different chemical structure from that of the sodium salts of the usual heterocyclic sulfonamides in that in sodium sulfasuccidine it is the succinyl portion of the molecule which is involved in salt formation The sodium salt has been used experimentally in testing the toxicity of sulfasuccidine but has not received clinical application

The clinical application of the drug has been proposed as an intestinal bacteriostatic agent particularly with reference to gram negative organisms and in preoperative preparation and postoperative treatment of patients requiring surgical procedure on the intestinal tract such as operations for carcinoma of the colon or rectum ileostomy fecal fistulae and so on

Pharmacology of Succinylsulfathiazole

In the pharmacological action of this compound the effective agent, at least in appreciable part, is free sulfathiazole The succinyl radicle presumably inhibits the absorption of the drug from the upper intestinal tract[5, 6] Lower in the intestinal tract the succinic acid is split off by hydrolysis either by the animal tissues or by the bacteria in the bowel liberating sulfathiazole which is comparatively little absorbed from the large intestine[5, 7] In usual oral doses very little is absorbed from the intestinal tract less than with sulfaguanidine and like the latter drug that which is absorbed is excreted very rapidly by the kidneys Unlike sulfaguanidine, however small repeated doses of the drug do not give any higher blood concentrations than large single doses When given to dogs in doses of 1 0 gm per kilo body weight which is approximately 4 times the dose recommended for humans a blood concentration of sulfathiazole of 3 5 mgm per 100 c c occurs and a urinary concentration of 360 mgm per 100 c c takes place Due to slight absorption from the gastrointestinal tract 5 per cent or less of the total dose is excreted by the kidneys The concentration in the feces under such circumstances is about 5 per cent of the water content That which is absorbed diffuses negligibly through body tissues, and when studied in rats and monkeys the absence of toxic effects on organs and tissues has been quite striking[5, 9]

The solubility of succinylsulfathiazole has been given as 60 to 70 mgm at 37° C in water, and 305 mgm per 100 c c in plasma at 37 5° C This is the solubility of sulfasuccidine as such since succinylsulfathiazole is already conjugated and it cannot be acetylated as such The acetylation, which occurs, is with the sulfathiazole fraction

When tests for concentrations of drug in blood and body fluids are carried out according to the method of Bratton and Marshall[9] the fraction determined is that of free sulfathiazole Determination of the concentration of the total sulfonamides that is free sulfathiazole plus unhydrolyzed succinylsulfathiazole plus any other derivatives in which substitution of the paro amino group has occurred, i e acetylsulfathiazole requires special treatment The blood filtrate or other material should be treated for about 2 hours at 100° C in the presence of approximately 1 5 normal sodium hydroxide 5 parts of filtrate plus 1 part of 40 per cent sodium hydroxide in order to insure complete liberation of the sulfathiazole component With the aid of phenolphthalein the excess of alkali is neutralized with 4N hydrochloric acid Excess of acid is added to give a concentration after the final volume adjustment of 0 2 normal Diazotization and color formation then are carried out in the usual manner

A simpler acid method for the determination of total sulfonamides with sulfasuccidine has been developed by Welch and associates[9] To the filtrate suffi

cient hydrochloric acid is added to make the concentration about 1N after heating at 100 C for 2 hours and volume readjustment diazotization may be carried out without neutralization of the excess acid

In dogs in which most of the studies have been carried out when given in adequate amounts sulfasuccidine causes a striking lowering of the stool count of *E coli* from an average normal of 10 000 000 per gram of wet stool to less than 1 000 per gram At the same time the character of the stools becomes profoundly altered the odor is almost completely lost and they become semifluid in consistency and contain more than the normal amount of mucus Diarrhea does not occur

In the monkey on the other hand where coliform bacteria were found not to be the predominating organism but lactobacilli streptococci and anaerobic bacilli existed succinylsulfathiazole had no effect on the total bacterial count of the feces If *B coli* are to be reduced in the stools of monkeys much larger doses are required than in the dog Welch and his associates attribute this difference possibly to the presence of substances either contributed by the non coliform organisms or by the intestinal secretions of the monkey which inhibit the anti coliform activity of the drug Such factors appear to be of little significance in humans An effect on growth rate in rats cannot be produced as easily as with sulfaguanidine but requires a highly purified diet in addition Furthermore sulfasuccidine does not seem to be influenced in its growth effects by para amino-benzoic acid as is sulfaguanidine [3]

In order to study the effect of ulcerating lesions upon the bacteriostatic action of the drug lesions were produced in the colon of dogs by destruction of the mucosa by pure phenol applied through a proctoscope The antibacterial action of the drug was not significantly diminished in the presence of such lesions It has been found that unlike sulfaguanidine sulfasuccidine seems to have an ameliorating effect on ulcerating intestinal lesions but is less effective in the presence of diarrhea

In man succinylsulfathiazole (sulfasuccidine) has effects very similar to those seen in the dog Within 1 to 7 days after the institution of treatment the feces become semifluid small in bulk somewhat gelatinous in appearance and relatively odorless As in animals the coliform count drops rather rapidly from an average of 10 000 000 per gram of wet stool to 1 000 Following the discontinuance of the drug the bacterial flora quickly returns to its normal high count

Sulfasuccidine is the most potent agent in the bowel of man against coliform organisms and the clostridia Of abnormal organisms the drug has been found to be very effective against Flexner Shiga and Sonne strains of dysentery bacilli but relatively ineffective against *F typhi E paratyphi Streptococcus fecalis alpha B proteus* and the salmonella group

Pharmacology of Succinylsulfathiazole

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colostomies and enterostomies the powdered form of the drug may be introduced directly into the bowel segment

In *dysentery* the use of sulfasuccidine has given generally encouraging results In the therapy of dysentery regardless of the type severe diarrhea inhibits some what the action of the drug Therefore it is essential to give an adequate dosage of opiates to check the diarrhea so the drug will not pass through the bowel too rapidly Crohn [3] has found deodorized tincture of opium in 5 minim doses or paregoric after every second stool helpful in checking diarrhea and promoting adequate drug concentration in the bowel

In Lyon s treatment of 14 cases of *Flexner* dysentery the results were equally as good as with sulfaguanidine [8] In 10 infants and children and 10 adults Poth Chenoweth and Knotts [14] report no failures and no deaths They found sulfa succidine therapy successful whether started early or late Fever subsided promptly and organisms disappeared from the stools in 48 hours *Shigella para dysenteriae* was especially susceptible to the action of the drug On the other hand Roberts and Daniels[113] failed to find striking benefit in 89 cases of shigellosis when compared with 136 control cases With or without sulfasuccidine therapy the fever persisted for 2 or 3 days and the diarrhea 4 days The drug produced no amelioration of the illness nor did it shorten its duration The carrier rate in the bacteriologically proved cases however was influenced In an untreated group the carrier rate was found to be 18 2 per cent but with sulfasuccidine this was decreased to 2 6 per cent [35]

In the treatment of *amebiasis* succinylsulfathiazole has met with some degree of success but the reports are very limited In 6 cases studied by Knotts and Thompson [16] the drug was thought to give marked subjective relief and apparent cure They used larger doses than those outlined however giving 8 0 gm (gr 120) as an initial dose repeated in 4 hours and thereafter 0 2 gm per kilo body weight daily in divided doses every 4 hours As an antidiarrheic calcium car bonate was given in 1 0 gm (gr 15) doses with each dose of sulfonamide In their observations they found that *Strongyloides stercoralis* and *Chilomastix* were unaffected by the drug

Crohn reports good improvement in 11 of 8 cases of chronic *idiopathic ulcerative colitis* and some improvement in 9 others treated with sulfasuccidine Because so called non specific ulcerative colitis has not been proven to be due to a bacterial infection this new drug probably is helpful against the secondary invaders present He found a drop to normal in the febrile course with the help of opiates cessation of diarrhea a return of appetite and rising hemoglobin values of the blood On the basis of the above criteria strictly applied 5 of his cases were cured at least temporarily One case of *actinomycosis* seemed to show definite improvement also Crohn [3] concludes that sulfasuccidine is not a pan

Clinical Uses of Succinylsulfathiazole

The aim in introducing a succinyl derivative of sulfathiazole was to further the study of preparations, which would not be absorbed from the intestinal tract to any great degree and to provide one which would be chemically effective even in the presence of ulcerating mucosal lesions Hence, as with sulfaguanidine it has been used particularly in the treatment of infections of the intestinal tract and pre and post operatively The substance, succinylsulfathiazole, is inert and in itself has no therapeutic value Its efficacy lies in the sulfathiazole hydrolyzed from it and the fact that the breakdown of the molecule occurs low down in the intestinal tract where sulfathiazole is not absorbed appreciably To be effective the drug should come into contact with all portions of the bowel mucosa when this is accomplished the desired effect usually is attained in from 3 to 5 days In the presence of enterostomies or diversion of the fecal stream or exclusion of various segments of the bowel by one means or another the drug may need to be introduced directly into each isolated segment

Succinylsulfathiazole is to be given by mouth, the dosage depending upon the condition being treated When used in the therapy of *dysentery* 5 0 gm (gr 7^{1}) as an initial dose, followed by 2 5 gm every 4 hours, is advisable In the absence of diarrhea 0 25 to 0 3 gm (gr 4 to 5) per kilogram may be given daily in 3 or 4 divided doses i e every 6 or 8 hours A maintenance dose of 0 .5 gm per kilo body weight per day should be administered until the temperature has been normal for 2 or 3 days and the stool cultures have become negative The dosage for children is the same as that for adults One of the disadvantages of this drug is the large doses that are required sometimes to obtain desired results

In its *preoperative* and *postoperative* use the patient should be placed on a low residue diet and given an initial dose of 0 25 gm of the drug per kilo body weight Thereafter maintenance doses are given on a basis of 0 25 gm per kilo body weight per day divided into 6 equal doses and administered every 4 hours No enemata or purgatives should be used At operation the bowel usually will be found to be collapsed and free from feces and gas With such preparation operation may be performed on the open colon without undue risk of peritonitis or local abscess formation providing well established surgical principles are followed scrupulously[53] The postoperative dose is continued on the same basis as the preoperative maintenance level that is 0 25 gm per kilogram Nausea and vomiting from the drug seldom occur It is advisable that treatment be continued for some time after operation, and if the drug is indicated it should not be withheld if it is at all possible for the patient to take water since the normal bacterial flora is rapidly restored upon withdrawal of the drug In the case of

mide compounds particularly sulfathiazole, but perhaps less often because of its more limited absorption The treatment of the toxic effects of succinylsulfathiazole is essentially the same as that outlined in the section on sulfaguanidine From the studies of Welch and Wright the use of supplementary vitamin K and biotin may have a place, when sulfasuccidine is used in the treatment of intestinal infections

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acea but expresses hope in its use as a good adjunct in the therapy of colitis In Plummer's[11] experience the clinical effect in chronic ulcerative colitis has not been impressive The results in acute diarrhea and in surgical cases have not been appraised fully, but he believes probably they will be no better than when sulfathiazole or sulfadiazine are administered orally or the sodium salts are given parenterally

From preliminary observations sulfasuccidine has not shown striking benefit in the treatment of *typhoid fever* It may ameliorate meteorism in some patients but has little effect in eliminating the organisms from the intestines From the studies of Sadusk and Oswald[174] theoretically sulfasuccidine should be a drug of choice in the treatment of *cholera* since in vitro studies show that sulfathiazole is the best drug against this organism, and since succinic acid is an acid and V *cholerae* grows poorly in an acid medium There are no clinical reports available at the present time however, to prove or to disprove such a contention

If succinylsulfathiazole is given for the treatment of intestinal infections and failure results the following factors may need to be considered If the drug fails to come into good physical contact with the mucosa, the desired results may not be attained Liquid petrolatum interferes somewhat with its antibacterial action Diarrhea inhibits its action also and should be controlled first Inspissated feces may prevent a complete effect Finally, although small ulcerative lesions may not prevent bacteriostasis large denuded areas retard the rate at which organisms are diminished in the intestinal tract

Toxic Effects of Succinylsulfathiazole

In the rather extensive studies of Welch, Mattis and Latven[537] using rats, mice and monkeys very little was found in the way of toxic effects from sulfasuccidine All the animals continued to gain weight, and blood, plasma protein, isoiodeikon studies of liver excretion and kidney function all remained within normal limits In Crohn's series there were also very few toxic symptoms manifested by his patients Loss of appetite was rather common, but nausea and vomiting were rare Occasionally headache and malaise were complained of Two cases developed secondary anemia, and 2 other cases had high fever with extreme exacerbation of their diarrhea but both subsided promptly upon discontinuance of the drug No durable harm or persistent untoward symptoms were noted Johnson[38] reports the case of a white boy of 19 with moniliasis of the skin and presumably of the intestine who was said to have reacted severely to a second course of sulfasuccidine with agranulocytosis and death Autopsy was not performed It is to be expected however when this drug receives more widespread use that much the same toxic effects will occur as with the other sulfona

mide compounds particularly sulfathiazole but perhaps less often because of its more limited absorption The treatment of the toxic effects of succinylsulfathiazole is essentially the same as that outlined in the section on sulfaguanidine From the studies of Welch and Wright the use of supplementary vitamin K and biotin may have a place, when sulfasuccidine is used in the treatment of intestinal infections

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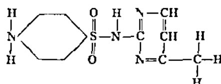
PART VI-B

SULFAMERAZINE SULFAMETHAZINE, SULFAPYRAZINE, PHTHALYL SULFATHIAZOLE

Sulfamerazine

A compound closely related both in structure and in its action to sulfadiazine is sulfamerazine It was first synthesized by Robin and his co workers who have done so much in the chemistry of the sulfonamide compounds while studying in 1940 various possibilities of chemicals derived from the sulfanilamide molecule[470] This comparatively new substance still is in the experimental stage of its devel opment but from its brief clinical application in medicine so far it holds promise of taking some place in the growing list of chemotherapeutic agents How major or minor a part it may come to play in therapeutics remains for the future At the time of this writing it can be said to be a very interesting substance though not yet accepted by the Council of Pharmacy and Chemistry for clinical applica tion

Chemically sulfamerazine is a pyrimidine derivative of sulfanilamide and is a methyl homologue of sulfadiazine It is 2 sulfanilamide 4 methylpyrimidine, sulfamethyldiazine and has the following structural formula



It will be seen that structurally when compared with sulfadiazine it has essentially the same formula plus the addition of a methyl radicle (CH_3) to the pyrimidine ring It is a white crystalline substance with melting point 230–231 C (uncorrected) and soluble to 35 mgm per 100 c c at pH 5 5, 45 mgm per 100 c c at pH 6 5 and 170 mgm per 100 c c at pH 7 5

In a rather extensive study of the pharmacology of sulfamerazine Welch and his associates[471] found certain interesting similarities as well as certain differences from sulfadiazine In animals and man when the two drugs are given in the same oral dosage sulfamerazine results in a higher blood level and more sustained blood concentration than sulfadiazine The blood level rises also more quickly with sulfamerazine The reasons for these differences are that sulfamerazine is ab sorbed more rapidly and more completely from the gastrointestinal tract, and it is excreted more slowly by the kidneys than is sulfadiazine By slow excretion is meant the relatively small amount which appears in the urine For studies

have shown that approximately 90 to 95 per cent of the drug that is excreted by the glomeruli is reabsorbed by the tubules It is this mechanism which accounts for the sustained blood level seen with sulfamerazine Furthermore the tendency of sustained blood levels with this drug may lend value to the use of sulfamerazine in the prophylaxis of certain infections These properties suggest that it may be possible to use sulfamerazine successfully in clinical practice on a basis of only one or two doses daily and that it may rarely be necessary to resort to intravenous injections of a sodium salt in order to attain blood levels quickly As will be brought out in the discussion of the clinical use of this drug however, Flippin and his associates[4 3] did find it of advantage to use the sodium salt intravenously in the treatment of seriously ill patients To put its pharmacological properties in another way the dosage of sulfamerazine required to produce high concentrations in the blood is usually about one-fourth to one half that which is required when sulfadiazine is used

The blood levels of the drug may be determined in the same way as for the other sulfonamide compounds after the method of Bratton and Marshall Welch[4 1] suggests the use of p toluenesulfonic acid in place of trichloracetic acid in the determination of pyrimidine derivatives of sulfanilamide He recommends a final concentration of 4 per cent p toluenesulfonic acid without added HCl which permits the hydrolysis of acetylated sulfamerazine within one hour at 100 C and gives good recoveries under controlled conditions The use of trichloracetic acid and hydrochloric acid seems to yield erratic results with totals often significantly lower than the free values

Further pharmacological studies have demonstrated that a single oral dose of 3 0 gm will give a blood level near 12 mgm per 100 c c at the end of 2 hours 13 5 mgm per 100 c c after 4 hours[47] The amount conjugated in the blood averages 15 per cent in 24 hours A single dose of 3 0 gm of 5 per cent sodium sulfamerazine intravenously gives a blood level of 19 0 to 20 0 mgm per 100 c c in one half hour but at the end of four hours the blood level for the three routes of administration oral intravenous and subcutaneous with the same dose is practically the same namely 12 mgm per 100 c c There is no absorption from rectal administration of sulfamerazine As has been pointed out with sulfadiazine a constant dosage of sulfamerazine tends also to maintain a constant blood level for that individual

Sulfamerazine penetrates inflamed meninges somewhat more readily than healthy ones In patients with meningeal infection on therapeutic doses the cerebrospinal fluid showed concentrations of 0 17 to 0 66 of that of the blood serum In normal persons given a single dose of 3 0 gm orally the spinal fluid ratio to blood serum was 0 1 to 0 17 at the end of 12 hours It is taken up more readily in pleural and ascitic fluids with ratios of 0 2 to 0 56 of the serum con

centration occurring after 12 hours. Studies on other tissues of cats (Shannon in work as yet unpublished) show that the ratio of distribution of sulfamerazine between tissue and blood plasma are much of the same order as for sulfadiazine. The figures given are for brain 0.35, red blood cells 0.45, lungs 0.56, liver 0.76, pancreas 0.47, muscle 0.39, nerve 0.50 and per cent of total body weight 45.8. These figures illustrate that the above tissue levels of drug are from one third to three fourths that contained in the blood stream.

The rate of urinary excretion of sulfamerazine is somewhat less than that of sulfadiazine. In creatinine clearance studies on dogs the excretion rate for sulfamerazine has been found to be 0.15 compared to sulfadiazine 0.35. In man similar studies have shown the ratio for sulfamerazine to be 0.21 and for sulfadiazine 0.33. The amount of acetylsulfamerazine recovered in the urine on a maintenance dosage remains practically constant at 50 per cent. Both the free and acetylated sulfamerazine are more soluble in the urine than sulfadiazine or its acetyl salt.

In a few preliminary clinical studies that have been carried out so far sulfamerazine seems to be effective in the treatment of those infections in which sulfadiazine has been found to be useful. It has been applied clinically in the treatment of pneumococcus pneumonia[4,5], meningococcus meningitis[47,4] and in a few cases of gonorrhea[47]. Whether it will be found to be effective in all the conditions in which sulfadiazine has been found to be helpful and any others remains to be seen.

In a series of 80 cases of *pneumococcus pneumonia* treated with sulfamerazine compared to 80 similar cases treated with sulfadiazine Flippin and his co workers[4,5] found the two drugs very comparable in effectiveness. The total amount of the drug necessary for cure of the disease was slightly less with sulfamerazine, however. The dosage administered consisted of 3.0 gm. (gr. 45) by mouth initially followed by 1.0 gm. (gr. 15) every 6 hours to some every 8 hours to others. When compared with the same dosage of sulfadiazine which gave average blood levels of 8 mgm. per 100 c.c. sulfamerazine blood concentrations averaged 10 to 12 mgm. per 100 c.c. A critical drop in temperature occurred in a few more patients and slightly sooner with sulfamerazine than with sulfadiazine. The little difference in mortality rates were slightly in favor of sulfamerazine, 7.5 per cent with sulfadiazine 10 per cent. This difference is statistically not significant. In 18 patients with bacteremia the mortality rate with sulfamerazine treatment was 33 per cent. As with other sulfonamide treated patients with pneumonia this drug seems at present to be no more efficacious against the complications than sulfadiazine, sulfapyridine or sulfathiazole. One patient developed endocarditis and died and another succumbed to meningitis during treatment.

During an epidemic of *meningococcus meningitis* Gefter and his co workers[474] treated a group of 45 patients with this drug with a mortality of 6 7 per cent This is very comparable to the present day figure with sulfadiazine treatment already discussed although these authors give their figures as 12 5 per cent mortality with sulfadiazine They began treatment in 36 adults with 3 0 gm (gr 45) of the 5 per cent sodium salt of sulfamerazine in distilled water intra venously followed by 1 0 gm (gr 15) by mouth every 4 hours In 9 cases in children they gave 1 0 to 2 0 gm (gr 15 to 30) of the sodium salt intravenously followed by 0 5 gm to 1 0 gm (gr 4 to 15) every 6 hours In delirious or comatose patients the drug was administered by nasal tube at the stated intervals until the patient was capable of taking it by mouth The drug was continued until the patient was entirely well clinically usually 10 days in adults and 8 days in children The average total dose required was 56 gm for adults and 20 gm for children Their methods of administration gave blood plasma levels between 13 and 16 mgm per 100 c c which seemed entirely adequate

The clinical improvement manifested first by mental clarity became apparent in 48 hours in three fourths of the cases Some fever usually persisted for several days following this initial response the patient becoming afebrile after 5 to 6 days In some fever persisted as long as 14 days Such complications as ocular palsies polyarthritis and Bell s palsy subsided completely under treatment

To 5 patients they gave antimeningococcus serum intravenously in addition to sulfamerazine but the added benefit derived therefrom was questionable From these brief studies there did not seem to be any remarkable advantages of sulfamerazine over sulfadiazine in its clinical effectiveness

In a limited number of cases sulfamerazine was considered to be inferior to sulfadiazine sulfathiazole and sulfapyridine in producing symptomatic and bac teriological cures of *gonorrhea* in the male[4] The results were better however 66 per cent than those for sulfanilamide 30 per cent The comparable figures given in this series for sulfadiazine were 83 per cent sulfathiazole 72 per cent and sulfapyridine 70 per cent The dosage scheme was not outlined More experience is necessary before any conclusions can be reached

Clark Flippin and Murphy[4 6] report the unsuccessful treatment of a patient with *subacute bacterial endocarditis* with massive doses of sulfamerazine After receiving 14 0 gm of the drug by mouth over a 3 day period 25 0 gm of the sodium salt intravenously over a period of 30 minutes produced a blood level of free drug of 106 0 mgm per 100 c c Over the course of the next 4 days without more of the drug the blood level remained above 10 mgm per 100 c c During the high blood levels the patient developed crystalluria hematuria and partial sup pression of urinary output but upon readministration of oral doses the urinary disturbances all cleared up

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are examples of such neurotropic toxicity The presence of a methyl group per se seems to offer no known chemical or pharmacological basis to justify a pre sumption that any sulfonamide containing a methyl group would be any more productive of nerve injury than one lacking such a group Welch and his co workers[471] paid particular attention to this possibility with sulfamerazine using dogs monkeys and chickens the latter having been found to show remarkable sensitivity to the nerve damaging potentialities of the sulfonamides[4 7] They found no evidence of nerve injury in dogs or monkeys in chickens the nerve lesions which occurred as the result of very high blood concentrations of sulfa merazine were of no greater severity than those resulting from lower blood levels of sulfadiazine with which comparison was made These authors conclude from their studies that it would appear reasonable to suggest that nerve injury fol lowing the clinical use of sulfamerazine should be no more frequent than follow ing sulfadiazine the preliminary use of the drug in human beings has disclosed no evidence of neuropathological changes

In the *treatment of the toxic effects* of sulfamerazine from the little which is known about this new drug it is reasonable to institute the same measures as described in the treatment of the toxic manifestations of the other sulfonamide compounds The adequate administration of fluids seems just as essential as with sulfadiazine Whether the administration of alkalies will be of benefit either in the prevention of toxic renal manifestations or in their treatment after they occur is not known at the present time Further developments concerning the clinical usefulness and possible toxic effects of this new drug are being awaited with a great deal of interest

Sulfametha ine

Sulfamethazine another recent sulfonamide compound has received some interest in Great Britain It is a dimethyl pyrimidine derivative of sulfanilamide dimethyl sulfadiazine In this compound there are two methyl groups replacing two hydrogens on the pyrimidine radicle with sulfamerazine there is one methyl group attached to the pyrimidine ring

A pale yellow crystalline material with solubility in water at 29 C to 150 mgm per 100 c c melting point 178–180 C (corrected) sulfamethazine pos sesses pharmacological properties and bacteriostatic effects essentially similar to those of sulfadiazine Its advantage from a chemical standpoint is its high solu bility but at the same time it places some limitation on its clinical usefulness. Whereas sulfadiazine is soluble to the extent of 12 to 110 mgm per 100 c c of water at 37 C in a pH range from 5 5 to 7 5 sulfamethazine under similar con ditions has a solubility of from 190 to 300 mgm roughly 10 times as soluble in the

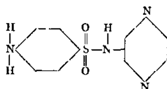
Very interesting and hopeful studies are being carried out with this drug in the treatment of *malaria*. At the time of this writing no definite results are available.

The preliminary studies so far suggest that perhaps sulfamerazine is no more productive of *toxic symptoms* than any of the other sulfonamide derivatives in common use today. In studies on animals Welch and his group[471] found some lessening of hemopoietic activity of bone marrow and minor changes in the liver in dogs and rather extensive renal tubular degeneration and dilatation of the kidneys in monkeys. There were no significant glomerular lesions however. Examination of the kidneys of 5 patients, who had died after sulfamerazine treatment including the patient given massive doses mentioned above, failed to show any renal damage which could be attributed to the drug.

In a series of 200 patients treated with sulfamerazine Clark and associates[470] found the over all toxicity to be 15 per cent. Hematuria was the most frequent complication, microscopic in 10 per cent of the cases, gross in 1.3 per cent. Nausea and vomiting occurred in 4.0 per cent, rash in 3.0 per cent, fever in 2.5 per cent, leukopenia in 2.0 per cent, psychoses in 1.0 per cent, and acute loin pain and thrombocytopenia each in 0.5 per cent of the series. A significant drop in hemoglobin and red blood cells seems not to have occurred and no cases developed agranulocytosis.

On the basis of the relatively greater solubility of both sulfamerazine and acetylsulfamerazine in the urine as compared to the sulfonamides now in common use, Welch and associates[471] and Clark and associates[470] have suggested that one might expect to encounter less urinary tract toxicity with this new compound. When one recalls the apparent paradox seen with the renal toxicity of sulfadiazine where it was predicted also to be less toxic to the kidneys because of the greater solubility of acetylsulfadiazine and yet as many as 15 per cent of cases showed crystalluria and 10 per cent microscopic hematuria, this new drug may not be as innocuous in its excretion as would be desired. Furthermore, the pharmacological studies so far indicate that it is just as necessary to force fluids with the administration of sulfamerazine as it is with sulfadiazine to prevent precipitation of the crystals in the urinary tract. More observations and studies are necessary before its proper place can be evaluated.

Another interesting question on the toxicity of this new compound from its chemical nature and pharmacological action concerns the possibility of untoward effects on the nervous system. It has been observed, as pointed out in other sections of this chapter, that in some instances the addition of a methyl group to the sulfonamide radicle caused the resulting compound to exhibit a greater potentiality for causing neuropathological changes than do the more simple sulfonamides. Sulfamethylthiazole, sulfanilyldimethylsulfanilamide and several others



This new compound at the time of this writing has not been accepted by the Council of Pharmacy and Chemistry Its pharmacological properties have been studied by Hamburger and his associates [4] In human subjects when 4 0 gm is given as a single dose an average blood level of 2 7 mgm per 100 c c is attained in 4 to 8 hours On a maintenance dose of 1 0 gm every 4 hours approximately the same blood level is attained as when sulfadiazine is given in doses of 1 0 gm every 6 hours Hence the absorption and maintenance level of sulfapyrazine are slightly less than with comparable doses of sulfadiazine The sodium salt of sulfapyrazine by mouth as with the sodium salt of sulfadiazine is absorbed slightly more rapidly with somewhat higher blood levels than is the sulfapyrazine The sodium salt monohydrate in distilled water used intravenously in doses of 4 0 gm gives blood levels varying between 10 and 16 mgm per 100 c c with rather slow excretion

Sulfapyrazine penetrates body tissues and fluids adequately but rather slowly Following administration of the sodium salt intravenously the spinal fluid is found to contain 50 to 60 per cent of that present in the blood after 12 hours This is in the case of healthy meninges Pleural and peritoneal fluids synovial secretion and fluid from the anterior chamber of the eye show concentrations approaching and sometimes exceeding that in the blood Breast milk and saliva contain only small amounts of the drug In treated patients the plasma concen tration of sulfapyrazine is approximately double that contained in the red blood cells In this respect sulfapyrazine resembles sulfathiazole and sulfadiazine dif fering from sulfanilamide and sulfapyradine which are distributed more uni formly

Sulfapyrazine is conjugated in the blood stream to about 5 per cent although in patients under treatment the proportion of combined drug was somewhat higher In the urine the amount of conjugated drug varies between 41 and 57 per cent

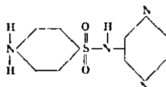
Approximately 70 per cent of the administered drug is excreted in the urine Its renal excretion is somewhat slow 35 to 50 per cent occurring in the first 4 hours another 0 to 25 per cent in the second 24 hours Its rate of excretion is somewhat similar to that of sulfamethylthiazole and somewhat slower than sulfa diazine As with sulfadiazine sulfapyrazine and acetylsulfapyrazine are many times more soluble in alkaline than in acid urine with the acetyl salt more soluble

acid range and 5 times as soluble in the alkaline range Acetyl sulfamethazine is nearly 5 times as soluble as acetyl sulfadiazine in the acid range but less soluble in the alkaline range namely 176 mgm against 248 mgm per 100 c c When an initial dose of 2 0 gm is given orally, the blood level rises rather promptly to 3 0 to 4 0 mgm per 100 c c in 2 hours, but due to its greater solubility it is excreted very rapidly in the urine When a larger initial dose is administered orally as studied by Rose, Martin and Bevan [44], a dose of 4 0 gm followed by 2 0 gm every 6 hours gives blood levels of 5 to 10 mgm per 100 c c To attain blood levels as high a 15 mgm per 100 c c, which may be necessary in severe infections requires large oral dosage combined with the sodium salt intravenously or intramuscularly Hence effective blood levels of the drug are somewhat difficult to maintain unless it is administered at frequent intervals or in large doses

Macartney and his associates[4 8] have used this drug successfully in the treatment of pneumonia meningitis and gonorrhea Jennings and Patterson[479] have given the drug clinical trial in children with fairly good results They seem to tolerate it well When given to adults in amounts of 4 0 gm (gr 60) as the initial dose followed by 2 0 gm (gr 30) every 6 hours an average blood level of 6 mgm per 100 c c occurs Conjugation amounts to only 10 to 15 per cent of the total at higher blood levels Sodium sulfamethazine is very soluble with a pH of 9 5 One gram (gr 15) may be injected intravenously in 3 c c solution without causing reaction When used in the treatment of meningitis the concentration of the drug in the spinal fluid rises fairly high between 50 and 80 per cent of that in the blood The toxic effects seem few mild nausea and vomiting disappearing while the drug is being continued A rather interesting feature in the series of Macartney and associates[4 8] was the fact that there were no crystals in the urine even though the concentration of the drug in the urine rose to high levels This feature may hold promise for this drug, but so far it has received no attention in this country If this drug has distinct value over any of the other sulfonamide compounds it warrants further trial

Sulfapyrazine

Sulfapyrazine 2 sulfanilamidopyrazine a para isomer of sulfadiazine is another recent sulfonamide derivative which is being tried in the treatment of some bacterial infections particularly pneumonia Sulfapyrazine was synthesized by Ellingson in 1941[539] and appears as a tasteless white powder, soluble to 5 2 mgm per 100 c c in water at 37° C The sodium salt with much the same characteristics is also a white powder and soluble to 5 6 mgm per 100 c c in water at 37° C The pH of sodium sulfapyrazine in 10 per cent aqueous solution is 9 3 Sulfapyrazine has the following structural formula



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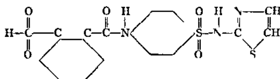
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Phthalyl Sulfathiazole (Sulfathalidine)

A new derivative of sulfathiazole phthalyl sulfathiazole is being developed by Poth[55] and his associates at the University of Texas for use as an intestinal antiseptic It is the basic molecule of sulfathiazole with phthalic acid added in the para amino position It has the following structural formula



Poth and his associates are proposing the name sulfathalidine for this new derivative which holds promise of having possibly certain advantages over sulfa guanidine and sulfasuccidine Two advantages in particular consist of the smaller dosage required to obtain similar results and the larger release of free sulfathiazole in the bowel than in the case of sulfasuccidine Perhaps the former is a result of the latter Sulfathalidine too has its chief effect in reducing the number of coliform organisms in the intestine producing the same relative decrease in bac terial count with only one fourth to one half the dose required by sulfasuccidine It is absorbed only very slightly by the intestinal tract and preliminary experi ments suggest that its toxic effects will be very minimal No clinical reports on the use of this new compound are as yet available however Augustine [3] has found it ineffective in experimental trichinosis

than the acid drug The dangers of crystalluria, however, are approximately the same as with sulfadiazine

Sulfapyrazine has had only limited clinical trial Schmidt and Sesler[541] compared the activity of sulfapyrazine against infections with beta hemolytic streptococci in mice with the activity of sulfanilamide sulfathiazole sulfapyridine and sulfadiazine and felt that sulfapyrazine was considerably more effective They attributed this efficacy to the ease with which an adequate blood level of the drug could be maintained but when the average blood concentrations were the same all five drugs were about equally effective against the strains of organisms used

Ruegsegger and his associates [4] have used this drug in the treatment of 105 cases of pneumococcus pneumonia with a resultant mortality of 4 per cent They used either 2 0 or 4 0 gm orally as an initial dose followed by 1 0 gm (gr 15) every 4 hours Later in the study they administered 4 0 gm (gr 60) as a 5 per cent solution of the sodium salt in distilled water intravenously followed by 1 0 gm (gr 15) every 4 hours by mouth They compared this therapy with the treatment of 133 similar cases with sulfathiazole in which the mortality was 7 per cent In 24 bacteremia cases there were only 4 deaths with sulfapyrazine, a mortality of 17 per cent They found the drug to be tolerated quite well, diminishing the signs of clinical toxicity very rapidly and causing a critical fall in temperature in 45 per cent of the non bacteremic cases As with the other sulfonamide compounds in the treatment of pneumococcus pneumonia sulfapyrazine produced a striking sterility of previously positive blood cultures

The *toxic effects* though somewhat less in this series were essentially the same as encountered with sulfadiazine therapy with the chief toxicity shown in the kidneys The toxic effects include nausea, vomiting fever, skin eruption crystalluria hematuria loin pain and nitrogen retention Cyanosis jaundice and major effects on the hemoglobin and red cells were not encountered One patient developed leukopenia 2 700 but 47 per cent polymorphonuclear cells remained present in the smear

In addition to withdrawal of the drug and forcing of fluids in the *treatment of the toxic effects* of sulfapyrazine Ruegsegger and associates [4] were able to decrease the incidence of toxic effects, particularly renal by diminishing the dose while at the same time obtaining clinical benefit This result was attained by giving a maintenance dose of 1 0 gm (gr 15) every 6 hours instead of every 4 hours

With this limited clinical data it may be said that sulfapyrazine seems to be effective in the treatment of pneumococcus pneumonia It does not appear to have any distinct advantages over other sulfonamides in more common use, particularly sulfadiazine Its effectiveness against other infections has not been studied as yet

The oral dose of tablets or capsules of neoprontosil less effective than sulfanilamide by mouth can be given over a longer period of time without toxic effects It has been thought that the therapeutic effect of this compound given orally probably is greater than when given parenterally because of its less rapid elimination in the urine The oral lethal dose of neoprontosil for laboratory animals has been found to be nearly seven times as great as that of sulfanilamide The oral dose required to produce a blood level of 7 to 10 mgm per cent is somewhat larger than for sulfanilamide When given by mouth like sulfathiazole it passes into the spinal fluid much more slowly than either sulfanilamide or sulfapyridine

The liquid neoprontosil has been used subcutaneously or intramuscularly It is marketed in two strengths 2½ and 5 per cent and either strength may be obtained in 5 c c. and 50 c c ampoules The 2½ per cent solution may be given either subcutaneously or intramuscularly yielding approximately 0 73–0 75 gm (gr 11–12) of sulfanilamide for 100 c c The dose for either route is up to 1 5 c c per pound of body weight in children weighing up to 25 pounds In patients weighing up to 120 pounds the dose is 1 0 c c per pound body weight per day These are maximum doses for patients severely ill For patients who are moderately ill 15 to 20 c c of the 2½ per cent solution injected every 4 hours often is sufficient This strength may be given intravenously also but it is not recommended because of its rapid excretion and because of discoloration of the skin Frequent bowel movements may occur after intravenous use of this drug The 5 per cent strength can be used intramuscularly in doses of 7½ to 10 c c every four hours for patients who are critically ill When given subcutaneously it may be very irritating

Clinically when given by mouth neoprontosil has been reported to be effective in the treatment of ulcerative colitis and in urinary tract infections lymphogranuloma inguinale and gonorrheal arthritis

There is little information on its toxicity It does not appear to be toxic when given by mouth probably due to poor absorption but the data are so scanty and fragmentary that no definite statements can be made

Three disulfonamide compounds have been introduced This has been confusing Named originally by the German makers as diseptal A B and C they are sulfanyl sulfanilamide (diseptal C) sulfanyl monomethyl sulfanilamide (diseptal B) and sulfanyl dimethyl sulfanilamide (diseptal A)

Sulfanyl sulfanilamide (diseptal C) also called disulfanilamide disulon

PART VII

Other Related Chemotherapeutic Agents

Of the many compounds related to sulfanilamide which have been introduced a few will be discussed briefly in an attempt to clarify some of the confusion that still exists None of them have been accepted by the Council on Pharmacy and Chemistry of the American Medical Association and several of them have been withdrawn from the market because of toxic effects A justification for their inclusion here is that from time to time results with them are reported and a ready reference concerning their properties usefulness and limitations should be available

Prontosil is a double benzene ring compound (4′ sulfonamide 2 4 diaminoazobenzene) and is the name of the original dye substance It is an unofficial drug and has not been accepted by the American Medical Association Council No exact chemical standards of purity have been established for it The drug consists of a red powder soluble in water to the extent of only 1 400 (0 25 per cent) It is converted partly to sulfanilamide in the body The therapeutic use of prontosil has been discontinued in the United States and it is not marketed at the present time in this country It is still in use in England however

Neoprontosil is the disodium soluble salt of prontosil This also is an unofficial drug for which exact chemical standards of purity have not been established It is a red dye (powder) containing three benzene rings (disodium salt of 4′ sulfonamido phenyl 2 azo 1 hydroxy 7 acetyl amino naphthalene 3 6 disulfonic acid) soluble in water to the extent of about 1 25 and marketed in tablets for oral use and in sterile solution (2½ per cent and 5 per cent) for parenteral injection It is known also as prontosil soluble and prontosil solution With either oral or parenteral administration absorption and excretion are somewhat irregular It breaks down in the body to release sulfanilamide and as far as can be determined sulfanilamide is the principal if not the only bacteriostatic substance released by this dye in the body Therefore it *is difficult to see how the administration of neoprontosil would offer any* advantages over the administration of the simpler compound sulfanilamide It has been used in preference to sulfanilamide where such conditions as hepatic insufficiency old age or intolerance to sulfanilamide have been present because it seems to be less toxic causing less nausea and vomiting but there is no convincing clinical evidence to support the claims that have been made for the greater therapeutic efficacy and the lesser toxicity of neoprontosil

The oral dose of tablets or capsules of neoprontosil less effective than sulfanilamide by mouth can be given over a longer period of time without toxic effects It has been thought that the therapeutic effect of this compound given orally probably is greater than when given parenterally because of its less rapid elimination in the urine The oral lethal dose of neoprontosil for laboratory animals has been found to be nearly seven times as great as that of sulfanilamide The oral dose required to produce a blood level of 7 to 10 mgm per cent is somewhat larger than for sulfanilamide When given by mouth like sulfathiazole it passes into the spinal fluid much more slowly than either sulfanilamide or sulfapyridine

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Sulfanyl sulfanilamide (diseptal C) also called disulfanilamide disulon

D B 32 is a double benzene ring compound which has been used extensively particularly in Europe Pharmacologically this drug is poorly soluble hence it is less readily absorbed and the blood level is less than with comparable doses of sulfanilamide It is excreted more rapidly in the urine than is sulfanilamide Experimentally it has been shown that this drug appears to have a certain degree of effectiveness in the control of streptococcal staphylococcal and meningococcal infections but in humans the results have not been as good as with sulfanilamide

There seems to be no doubt that sulfanyl sulfanilamide has a certain degree of efficacy in the treatment of gonorrhea in either sex Numerous European observers have claimed results superior to the use of sulfanilamide 85 to 95 per cent but American workers have not substantiated this Both good and poor results have been reported from the use of 1 5 to 3 0 gm (gr 22 5 to 45) a day for anywhere from 6 to 21 days The recent practice in Germany where this drug has been used most extensively is to give 2 0 to 3 0 gm (gr 30 to 45) daily for a period of one week then a rest period of seven to fourteen days followed by another week of treatment This regimen is based on the observation similar to that of Cokkinis and McElligott[250] as discussed under the sulfanilamide treatment of gonorrhea namely that better results are obtained if a few days are allowed to elapse before treatment is instituted to allow body immunity to develop Because of the moral laxity of many patients with gonorrhea such interrupted treatment may be a dangerous practice for it may help to spread an infection which has not been cured but is only dormant Good results with this drug in the treatment of gonorrhea have been reported using 3 6 gm (gr 55) a day for two days 2 4 gm (gr 36) a day for three days then 1 2 to 1 5 gm (gr 18 to 22 5) a day for another ten to fourteen days If the urine still is cloudy after the first five days of treatment one may use 1 8 to 2 1 gm (gr 27 to 32) a day until the urine becomes clear then reduce the dose The use of sulfanyl sulfanilamide has been advocated chiefly in patients with gonorrhea resistant to sulfanilamide

If sulfanyl sulfanilamide should prove to be as effective as sulfanilamide in the treatment of gonorrhea its distinct disadvantage is the toxic action of causing a *peripheral neuritis* Many such instances have been reported not only in Europe but in this country as well Rosenthal[51] has suggested that this complicating polyneuritis in humans after sulfanyl sulfanilamide resembles in many respects the neuritis caused by triorthocresyl phosphate There may be partial recovery which may be helped by the administration of thiamin chloride (vitamin B_1) The paralysis may become permanent however Harris and Michel[4] suggest

from their studies that there is a greater tendency to methemoglobin formation following sulfanyl sulfanilamide than with sulfanilamide Nelson[34] found peculiar doubly refractile radially striated crystalline bodies *in the kidneys of rabbits after administration of this drug*

Sulfanyl monomethyl sulfanilamide (diseptal B) known also as D B 87 has not been used clinically

Sulfanyl-dimethyl sulfanilamide (diseptal A) is also known as uleron (England) and ultron (U S A) as D B 90 and D B 373 It is related chemically to sulfanyl sulfanilamide with the addition of two methyl groups to a sulfonamide radical It is a colorless substance with a slightly bitter taste difficultly soluble in water but readily in alkaline solvents In its pharmacology it is very similar to sulfanyl sulfanilamide and like that drug has been used chiefly in the treatment of gonorrhea Marquardt[53] has found that when sulfanyl dimethyl sulfanilamide is given *to human beings about two thirds of it is excreted in the stools and* only one third in the urine It is not broken down to sulfanilamide in the body *With sulfanyl-dimethyl sulfanilamide the interrupted treatment* method has seemed to produce the best results Felke[54] prescribed 1 5 gm (gr 22 5) of the drug daily for six days followed by a five day rest period if the patient was not cured then he gave further courses of 2 0 gm (gr 30) a day for four day periods Cokkinis and McElligott have had good results with the use of this drug in the treatment of gonorrhea in women Its toxic effects are similar to those of sulfanyl sulfanilamide with a tendency particularly to polyneuritis Peripheral neuritis following the use of sulfanyl dimethyl sulfanilamide occurs more frequently in women and in ambulatory patients Walking standing and cycling are perhaps factors Myalgia and pruritis also occur Engelhardt *and Hullstrung[55] have been able to prevent neuritis following* the administration of this drug in pigeons by the simultaneous use of *thiamin chloride* (*vitamin* B_1) *This may be effective in the treatment* of a complicating neuritis in human patients if used early and in large doses

Benzyl sulfanilamide is a double benzene ring compound known also as septazine soluseptazine and proseptasine Benzyl sulfanilamide is poorly soluble and very little is known of its absorption or excretion It is less toxic than sulfanilamide and its action is not due to reduction to sulfanilamide in the body *Nothing is known about what concentra* tion in the blood or in other fluids is obtainable or is necessary or whether lack of toxicity is due simply to slow absorption owing to insolubility

This drug has been used chiefly in Europe in infections such as cellulitis erysipelas tonsillitis scarlet fever meningococcus infections and

actinomycosis In the treatment of 180 cases of erysipelas Bloch Michel Conte and Durel[6] gave 1 5 to 2 0 gm (gr 22 5 to 30) of benzyl sulfanil amide per day until the temperature remained normal for twenty four hours then 1 0 to 1 5 gm (gr 15 to 22 5) a day until the lesion was practically gone then 0 5 gm (gr 7 5) a day for another seven to four teen days They report only nine deaths In 150 patients ill with scarlet fever Peters and Havard[57] thought that this drug decreased the incidence of complications when compared to a control group It did not have much effect however on the scarlatina Later reports as by Mitman[5] were not as favorable Benzyl sulfanilamide has been advocated as a prophylactic agent in the control of puerperal infections

Soluseptasine is the soluble product of benzyl sulfanilamide marketed in ampoules It is a colorless substance which seems to be completely non toxic Experimentally it is effective against *Streptococcus hemolyticus* but not the meningococcus Soluseptasine probably is broken down to sulfanilamide in the human body

Sulfamethylthiazole 2 para aminobenzene sulfonamide 4 methylthiazole differs from sulfathiazole in having a methyl group attached to the carbon in position 4 in the thiazole nucleus Such methylation seems to increase its toxicity approximately 50 per cent over sulfathiazole In vitro studies of the different sulfonamide compounds showed that in its actions sulfamethylthiazole was very similar to sulfapyridine and sulfathiazole when used in the same blood concentrations In general the bacterio static action of sulfamethylthiazole has been found to be slightly but measurably less than that of sulfathiazole but somewhat greater than sulfapyridine It has been found to be even bactericidal for *Streptococcus fecalis* The excretion of sulfamethylthiazole in the urine is less than that of sulfanilamide sulfapyridine and sulfathiazole About 60 per cent of it is excreted in the urine Acetylation of the drug is not very great The crystals of sulfamethylthiazole in the urine may be mis taken easily by laboratory technicians for phosphates and urates The crystals are composed of the acetyl salt

The majority of reports of the use of sulfamethylthiazole have been with studies in vitro and in vivo in animals Clinically it has not been employed extensively because of a relatively high incidence of lower motor neurone involvement following its use which has caused its with drawal from the market

Various reports[9–63] have appeared on the use of sulfamethylthia zole The results in this miscellaneous series were on the whole quite good but because of certain toxic effects the authors concluded it was a drug to be used only in very severe infections

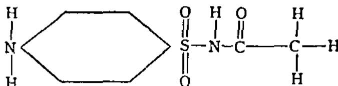
In the way of toxic manifestations jaundice skin rash granulopenia kidney and liver damage have been reported The minor toxic effects as nausea and vomiting seem to occur less frequently and less severely than after sulfathiazole but the most untoward effect of sulfamethyl thiazole has been upon the nervous system principally a lower motor neurone involvement which has been spoken of usually as a peripheral neuritis It occurs not uncommonly after several of the more complex sulfonamide compounds and is characterized by muscular weakness The condition is seen most often in the legs but has been reported in the arms and hands frequently bilateral and there may be muscular pain but usually muscle tenderness and disturbance of pain touch or temperature sensation are absent Hence the lesion is more in the nature of a pure motor weakness and not of a sensory nature It may occur during the administration of the drug or may have its onset as long as two weeks after the medication has been stopped A good chance of recovery may be obtained by the administration of thiamin chloride and the use of physical therapy

In a comparative study of the ability of all these compounds to produce injury to the nervous system of the chicken[264] sulfamethylthiazole was surpassed only by uliron and sulfaphenylthiazole This seems good reason for not using sulfamethylthiazole in treatment

Roseman and Aring[265] report an interesting case of hemorrhagic encephalitis in a 32 year old negro following the oral administration of sulfamethylthiazole The pathological picture was unique because ordinarily in hemorrhagic encephalitis the localization is confined chiefly to the white matter whereas in this case the perivascular hemorrhages were confined rather rigidly to the gray matter of the cerebral hemispheres and to the gray structures of the brain stem There were profound alterations in the small blood vessels chiefly of the endothelium and severe anoxic neuronal damage Toxic psychosis has occurred also with this drug

Sulfacetimide represents the most recent of the sulfonamide drugs in chemotherapy It was introduced originally by Young and his associates[266] in a study of its toxicity and effectiveness in the treatment of gonorrhea and urinary tract infections

When sulfanilamide passes through the body it is acetylated at the amino group attached to the benzene ring resulting in acetylsulfanilamide which is of low toxicity and of low therapeutic value In the laboratory it is possible to acetylate the amino group attached to SO radical to produce p amino benzene sulfonyl acetyl imide (sulfacetimide) Its structural formula is



It is a white crystalline powder odorless with slightly acid taste and melting point 181°–182° C soluble in water at room temperature about 1 100 Sulfacetimide is absorbed rapidly into the body is distributed widely in body fluids and tissues and is excreted largely unchanged by the kidneys The drug disseminates rapidly into the spinal fluid reaching a level somewhat lower than that of the blood It is eliminated from the blood stream rapidly in 72 hours

At the present time no extensive statements or results can be given concerning the use of this drug but only remarks in a preliminary way The drug is being made available in 0 5 gm tablets (7 5 gr) and in powder form It has been used only orally It is to be given 2 0–3 0 gm (gr 30–45) as an initial dose followed by 1 0 gm (gr 15) every four or six hours using preferably not more than 6 0 gm (gr 90) per day When given in larger amounts toxic reactions are apt to follow The average blood level of patients receiving 4 0 gm a day will be about 3 85–4 0 mgm per cent and on 6 0 gm a day 5 5 mgm per cent of the free drug On 4 0 gm a day one case of Young s reached a level of 13 6 mg per cent Any blood level above 12 mgm per cent seems to be definitely toxic

Comparing parallel concentrations of *sulfacetimide* with *sulfanilamide* in vitro Young and his co workers found sulfacetimide to be definitely superior in the case of *Staphylococcus aureus Gamma streptococcus fecalis, Escherichia Aerobacter* and *Proteus* The two drugs were equally ineffective against *Pseudomonas pyocyanea* Urine was the culture medium used In the treatment of 15 patients with *urinary tract infections* sterile urine cultures were obtained in 7 In six of the cases in which the drug failed a mixed infection was present The authors used 4 0 gm each day after an initial dose of 3 0 gm continuing for not less than two weeks and not more than three weeks In a large series of cases of urinary tract infections treated by Welebir and Barnes the drug was found to be useful In 40 cases of acute cystitis and 55 cases of chronic cystitis including upper urinary tract infections due to E (B) coli the results were 92 5 per cent improved in the former and 91 per cent

in the latter In 105 other cases with mixed infections the results were 80 per cent recovered and 17 per cent more improved In 8 cases of acute pyelitis of pregnancy cure was obtained The authors used from 16 to 28 gm in divided doses over 14 days In their study of urinary tract infections these authors felt that sulfacetimide was most efficacious against bacillary organisms but not as good as sulfathiazole against coccal infections

Young and his group studied also the effect of this drug on the gonococcus on chocolate agar plates in a CO_2 medium In the concentrations of drugs employed no differences could be observed between the action of sulfacetimide and sulfanilamide on the gonococcus

In the treatment of 29 cases of *gonorrhea* with this drug 15 (51 6 per cent) responded satisfactorily and in the remaining 14 cases the drug was ineffective Although this is a small series sulfacetimide in gonorrhea does not appear to be as successful as sulfathiazole Due to its lower toxicity however further trial may be warranted in patients who are sensitive to other sulfonamides or who have developed a drug resistant strain of gonococcus while being treated with one of the other compounds

The toxicity of sulfacetimide seems to be low In Young s series of 105 consecutive cases 6 or 5 7 per cent had pronounced reactions In two of these the reactions were induced intentionally (9 to 12 gm a day) in order to test the patient s tolerance In three others previous sensitivity had been demonstrated to other sulfonamide drugs These marked reactions included severe headache nausea vomiting dizziness nitrogen retention chills fever a red erythematous type of rash over the arms and edema of the face and hands In all of these cases the symptoms promptly disappeared upon withdrawal of the drug In 26 cases 8 (30 7 per cent) developed a slow drop in hemoglobin averaging 17 45 per cent This was transitory and no lasting effects on the hematopoietic system were noted In 21 cases in which the CO_2 combining power of the blood was determined a depression as low as 38 vol per cent was found in 20 This also was transitory No attempt was made to prevent it as by the administration of sodium bicarbonate

A uniform depression in the action of the enzyme carbonic anhydrase was noted in 10 cases in which this was studied The enzyme activity was depressed simultaneously with a lowering of the carbon dioxide combining power to values between 40 and 50 volumes per cent The authors state that this inhibition of the enzyme explains the necessity for administering large doses of bicarbonate in order to combat acidosis From this they suggest a new differentiation of acidosis namely a division

into those cases in which the enzyme carbonic anhydrase is or is not inhibited Sulfacetamide is inhibited also by p aminobenzoic acid

In two cases in this series there was a slight rise in the blood chlorides no cases of leukopenia or no cases of urinary suppression were observed

Promin is the name that has been given to the sodium salt of p p[1] diamino diphenyl sulfone N N[1] dextrose sulfonate introduced for intravenous use in the treatment of streptococcal infections and hopefully for the therapy of human tuberculosis It is not yet on the market

When given by mouth it is absorbed erratically and causes frequent anorexia mild delirium and a dusky slatish type of cyanosis When given subcutaneously it causes burning and discomfort Its greatest usefulness has been found to be by intravenous administration Even with this route it gives rise to momentary nausea in about 20 per cent of cases

In a careful study of 154 patients treated with this drug by intravenous administration Toomey and Roach[267] used 5 0 gm (gr 7_5) three times a day for three days irrespective of age weight or sex It is to be injected slowly The blood levels with this dosage vary somewhat but fall usually between 4 and 10 mgm per cent These authors used the drug only in streptococcal infections including tonsilliti sinusitis and pharnygitis It seemed to be especially good in the treatment of upper respiratory tract infections Of the entire series 82 per cent are reported as responding favorably the poor results occurring in cases that had scarlet fever as a complication

Promin has been used also in the treatment of one case of lupus erythematosus with failure[127] and it has been ineffective in gas gangrene when given locally orally or combined to rabbits infected with Clostridium Welchii

Some preliminary suggestions have been offered to the effect that this drug holds promise of being effective in the treatment of human tuberculosis The drug is obtainable only for experimental use and no satisfactory reports have appeared The results will be awaited with great interest

Toomey and Roach have considered promin in equal dosage to be less toxic than sulfanilamide and tolerated better than either sulfanilamide or sulfapyridine In their cases it had no significant effect on the blood elements and did not cause concretions in the urinary tract It appeared to have no synergism with sulfanilamide or sulfapyridine

A sulfanilamide derivative called *N[1] dodecanoyl sulfanilamide* was synthesized by Crossley Northey and Hullquist in 1939 and proposed as a possible chemotherapeutic agent against tuberculous infections It

has been shown to be capable of inhibiting human tubercle bacilli in vitro and of arresting the spread of tuberculous infections in guinea pigs It has failed to exert any inhibitory effect on bovine tuberculosis in rabbits Results in humans have not been published

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PART VIII

Local Use of the Sulfonamide Compounds

Since the introduction of the sulfonamide compounds applied in the treatment of systemic diseases two new principles in their use have been introduced The first discussed under sulfaguanidine is the concept that a drug given per os can be quite soluble in the stool while at the same time its absorption from the gastrointestinal tract is limited The second concerns the local application chiefly of a powder form into wounds and tissues Originally sulfanilamide in solution 1 0 per cent was tried locally for throat irrigations for irrigation of pleural cavities septic wounds etc but with no uniform success Gargles and throat irrigations were proved to be useless the opinion in the other conditions was divided In the summer of 1939 Jensen and his coworkers at the University of Minnesota[23] pioneered a new field introducing the powder of sulfanilamide into the wounds of compound fractures The remarkable success reported by them stimulated many studies and applications of this method with the result that local treatment has become widely used in many different types of conditions Although the powdered form of all of these drugs is available sulfanilamide and sulfapyridine so far have received the greatest study The reason is for sulfanilamide particularly the greater solubility of its powder in tissue fluids The major portion of this discussion will be concerned with sulfanilamide Undoubtedly in the future the powdered form of the other compounds will find their respective places in local application

The value of local application of these drugs lies in the high concentration that can be attained to act both bacteriostatically and bactericidally on the invading organisms The maximum concentration which occurs in a wound immediately adjacent to the inserted drug depends upon the solubility of the substance in the wound fluids Since such fluids are albuminous the solubility in them should approximate that in serum although in some wounds the reaction may be more acid On the basis of solubility the various compounds would be effective locally in approximately the following order based on solubilities per 100 ml at 37° C sulfanilamide 1 500 sulfaguanidine 220 sulfathiazole 184 sulfadiazine 124 and sulfapyridine 61

When applied locally the effect of the drug is on both bacteria and tissues and will depend upon the cleanliness of the area presence of foreign body the local blood supply and the amount of powder used

In an unclean wound with peptone of tissue breakdown present there is a decreased bacteriostatic effect of sulfanilamide This may be overcome by careful débridement and cleansing of the wound or by the use of larger amounts of the powder This latter then acts as a foreign body to be discussed subsequently

The results of numerous studies indicate that sulfanilamide travels quickly from one part of a wound cavity to another that it will diffuse slowly through dead tissue and that its local penetration into tissue with an active circulation does not extend more than 2 to 3 mm The other compounds studied produce lower concentrations in the distal parts of a wound their order in diminishing effect being sulfathiazole sulfaguanidine sulfadiazine and sulfapyridine Both sulfathiazole and sulfapyridine diffuse through dead tissue at a very slow rate Both resemble sulfanilamide in their restricted penetration into tissue with an intact circulation

When sulfanilamide is placed in a wound appreciable absorption occurs into the blood stream Such levels usually are not high enough to occasion any alarm but if the drug is applied heavily blood concentrations approximating those produced by oral administration may result and hence the same toxic effects are to be expected One should employ caution in the simultaneous local and oral or parenteral use of the drug Where the local blood supply is intact more absorption will occur than from ischemic tissues If the wound is bleeding freely small amounts of the powder will act as a hemostatic large amounts on the other hand act as a foreign body with resulting continuous oozing both of blood and tissue fluid

The sterilization of sulfanilamide powder for local use is desirable but is not mandatory No instances of infection as from spore-forming organisms seem to have occurred Nevertheless sterilization is desirable and may be carried out by placing given amounts such as 4 6 or 8 gms in cork stoppered test tubes with the application of dry heat for ½ hour at 120 C [9] The powder may be autoclaved at 15 pounds pressure for 30 minutes placed in a vacuum for 10 minutes and dried This method advocated by Key[169] causes a yellowish discoloration of the powder but no untoward effects seem to be caused by this

The *dose* of the powder *to be applied locally* has been described variously As a basis for administration Lyons has suggested 0 1 gm (gr 1½) per square inch of exposed tissue Others have advised the use of 1 to 2 gm for small wounds and doses as large as 15 to 20 gm for large cavities such as the peritoneal A good descriptive rule has been given by the English workers namely the sprinkling of the powder lightly

and evenly to resemble hoar frost It has been suggested that the wound be dry upon application of the powder then the powder is to be moistened immediately with saline covered with saline gauze and oiled silk On an external wound as experienced in the European war if a thin film of dry exudate forms in only several minutes the bacteriostatic effect is lessened Such local application results in a tissue concentration of 500 to 1 000 mgm per cent The rate of absorption the knowledge of which is necessary to determine the frequency of application varies somewhat depending upon the tissue In a local wound as of an extremity with its muscle and fat the drug is dissolved slowly reaching a peak of absorption in approximately 18 hours and continuing frequently for more than 30 hours Under such circumstances a dressing changed once a day may be sufficient From a serosal surface as from peritoneum or pleura the absorption is much more rapid reaching a peak in 2 to 3 *hours with very high blood levels resulting in less than 4 hours This* is in experimental animals usually with a healthy peritoneum With a diseased peritoneum with its increased vascularity as in *E (B) coli* peritonitis in dogs the writer with B Steinberg has observed an increased absorption that is 15 to 25 per cent greater than from a normal peritoneum Clinically as well as experimentally there is tremendous variation in absorption from the peritoneum and excretion of the drug By this route severe toxic effects such as jaundice result from extremely high levels in the portal vein and its burden upon the liver

In average amounts applied locally sulfanilamide does not harm even the most delicate tissues When applied to the edges of clean wounds in the skin scalp mucous membranes stomach intestine bladder etc. healing usually is prompt In larger amounts it can be irritating to fat and subcutaneous tissue Also it is not irritating to bone very little is absorbed from it In excessive amounts it acts as a foreign body with continued oozing and bleeding and failure of tissue to heal

In *orthopedic surgery* this method of application had its initial trial and has been used very successfully In Jensen s original description of the treatment of *compound fractures* the method consisted of thorough debridement immediate reduction careful hemostasis followed by the introduction of 5 to 15 gm (gr 75 to 225) of crystalline sulfanilamide into the wound with primary closure of the skin avoiding tension Complete immobilization was maintained by traction and plaster splints where applicable In 39 compound fractures treated by this method there were no instances of secondary infection whereas in 94 open fractures treated by similar methods except that sulfanilamide was not used there was an incidence of 27 per cent. infection In extensive studies

carried further by Key and his associates the legs of dogs and rabbits were fractured and the drug was applied locally into the wound muscle tendon and joint and when compared to controls all wounds healed by primary intention with no delay in union and with no tissue reaction In the case of infected wounds thorough cleansing and debridement are essential Key favors the use of a mixture of sulfanilamide and sulfathiazole for one of the disadvantages of sulfanilamide alone is its lower bacteriostatic activity against many of the organisms which may be present The amount to be used is 3 to 5 gm of the powder This method is effective also in *acute pyogenic arthritis* in which the joint should be opened washed out with physiological saline the powder implanted and the joint left open In mild infections the joint may be closed and immobilized In *chronic osteomyelitis* the powder applied locally decreases the purulent exudate and promotes callus and granulation tissue formation In these various circumstances the drug may be given by mouth as well

In *small wounds* and particularly in *undermining ulcers* as of the legs sulfanilamide in combination with other local therapy has proved to be very effective Most useful of the other agents employed have been hydrogen peroxide and zinc peroxide Based on the bacteriological work discussed under mode of action of these drugs namely the availability of oxygen aiding sulfonamide action both forms of peroxide have been used particularly where anaerobic organisms are present Sulfanilamide has little or no antibacterial effect on anaerobic streptococci and with these present Meleney and Harvey[170] found that a combination of zinc peroxide used locally with sulfanilamide given orally and also used locally was more effective in cases of undermining *ulcers* than either substance alone More recently Schneider[164] washed wounds out first with hydrogen peroxide and then applied 2 gm sulfanilamide suspended in 30 c c hydrogen peroxide This method will bear further trial

As the reports however fragmentary are appearing from war torn Europe there is every indication that the local use of the sulfonamides is extremely helpful not only in the active treatment of ragged wounds but in prophylaxis Colebrook has reported that the local use of sulfanilamide applied early in all kinds of *war wounds* markedly reduces the incidence of gas gangrene and other types of infections It is unfortunate that in spite of the fact that sulfanilamide packs were used in the treatment of several hundred war wounds in France in the chaos that followed Dunkerque no accurate data could be obtained However various observers were in general agreement that the drug was beneficial when applied locally Those wounds that had a sulfanilamide pack looked

and evenly to resemble hoar frost It has been suggested that the wound be dry upon application of the powder then the powder is to be moistened immediately with saline covered with saline gauze and oiled silk On an external wound as experienced in the European war if a thin film of dry exudate forms in only several minutes the bacteriostatic effect is lessened Such local application results in a tissue concentration of 500 to 1 000 mgm per cent The rate of absorption the knowledge of which is necessary to determine the frequency of application varies somewhat depending upon the tissue In a local wound as of an extremity with its muscle and fat the drug is dissolved slowly reaching a peak of absorption in approximately 18 hours and continuing frequently for more than 30 hours Under such circumstances a dressing changed once a day may be sufficient From a serosal surface as from peritoneum or pleura the absorption is much more rapid reaching a peak in 2 to 3 hours with very high blood levels resulting in less than 4 hours This is in experimental animals usually with a healthy peritoneum With a diseased peritoneum with its increased vascularity as in *E (B) coli* peritonitis in dogs the writer with B Steinberg has observed an increased absorption that is 15 to 25 per cent greater than from a normal peritoneum Clinically as well as experimentally there is tremendous variation in absorption from the peritoneum and excretion of the drug By this route severe toxic effects such as jaundice result from extremely high levels in the portal vein and its burden upon the liver

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Various other pastes and ointments have been devised several of which use cod liver oil or hydrous wool fat base which seems to be more satisfactory for incorporating the powder Spink suggests the following

Spermaceti	50 0
White wax	200 0
Lanolin (anhydrous)	250 0
Sulfanilamide	250 0
Water	1 250 0
Aquaphor *	3 000 0

Aquaphor is a proprietary base claimed to be superior to pharmacopoieal bases particularly in its ready miscibility with three times its own weight of water

Melt the spermaceti and wax add lanolin and aquaphor and melt sufficiently to permit thorough mixing add water gradually while mixing Sprinkle sulfanilamide in portions over top of preparation and continue mixing until smooth paste is obtained

Guyton[75] has described an ointment that seemed particularly good for application to mucous surfaces After extensive trial however it was found to be not always uniform and smooth So the formula was modified to consist of sulfanilamide or sulfathiazole alone in a very fine powdered form mixed into a petroleum lanolin base (Guyton)

Veal and Klepser[76] have devised a greaseless ointment prepared as follows

Sulfanilamide	10 per cent
Allantoin	2 per cent
Chlorobutanol	0 5 per cent
Greaseless base	q s 0 per cent (glycerinated stearic acid ointment with triethanolamine)

Although such ointments are the preferred method of application locally of sulfanilamide to burns any of them may be used successfully in any external application of the drug to wounds ulcerations etc

Recently Pickrell at the Johns Hopkins Hospital[77] used sulfadiazine successfully locally in the treatment of 100 ambulatory and 15 hospitalized patients with burns The two types of patients were treated differently The hospitalized patients were placed on sterile sheets and without washing or cleaning the burned areas the wounds were sprayed with 3 per cent sulfadiazine in 8 per cent triethanolamine in an atomizer The first day the wound was sprayed every hour the second day every two hours the third day every three hours and the fourth day every four hours This procedure gives a thin pliable elastic and translucent

cleaner after an interval of 5 days than those that had no sulfanilamide Experiments are reported as being attempted to produce sticks crayons of sulfanilamide and an emulsion of the drug in the form of a paste that can be squeezed out of a tube to be supplied to each soldier

As discussed under sulfanilamide, the internal use of this drug in *gas gangrene* has not always been successful However in a few reports mostly from England the local application of this drug has seemed very effective in gas gangrene Buttle has remarked[271] that although the cases were not numerous the results have been so good that the extensive amputations commonly necessary in the last war for this condition may be largely avoided In some interesting experiments in animals Reed and Orr[272] found local powder better than oral or combined Incisions were made into the thighs of rabbits with the insertion of dead tissue sterile garden soil calcium salts blood clots and the various organisms *Cl Welchii Cl septique Cl sordellii* and *Cl novyi* Sulfapyridine and sulfathiazole were better than sulfanilamide and yet local treatment with sulfanilamide was far superior to that by mouth

These drugs however have not been found to be especially effective against clostridia so for the present it would seem that every effort should be made in the way of prevention of gas gangrene with debridement the use of antiserum when available and the application of sulfanilamide for its action particularly against secondary invaders upon which it is known to be effective The dose to be applied is 5 to 15 gm into the wound When staphylococci are present the use of sulfathiazole in cod liver oil appears to be very promising[273]

Sulfanilamide locally has been found to be effective in the treatment of *burns* Because of the drying effect of the powder on burns an ointment of it seems to possess definite advantages Such a paste called euglamide has been devised by Robson and Wallace[274] It is prepared by mixing 5 gm soluble albucid (acetylsulfanilamide) powder with 100 c c glycerine then this is heated cautiously for 30 minutes until the solid is completely dissolved The heat next is discontinued and while the mixture still is warm 10 c c cod liver oil is added while stirring thoroughly This solution is mixed into a quantity of fine kaolin about 80 gm sufficient to yield a smooth paste of the consistence of thick cream In applying such a paste a thick spread is made on sterile white lint gauze or linen and covered with a wool bandage In burns about the face and in the region of flexures dressings are reapplied daily but for other parts they may be kept on for 3 days If infection is present the part is wiped clean with normal saline or cod liver oil and the dressing changed daily regardless of site

even being tried as a snuff for head colds and upper respiratory infections but without much success. Only a few of these will be discussed. The powder has been applied in the wounds of herniorrhaphies with rapid healing *without infection and with retention of apparently normal tensile* strength of the scar. Studies of its application to the brain in neurosurgery have shown this to be a safe procedure. At first it may cause a slight focal meningeal leukocytic response which disappears promptly. Microscopically some crystal particles may remain which become encased by foam cells. Absorption of the drug is quite rapid and by comparison it seems to cause less tissue reaction than silk or silver clips.

In dentistry the local application of sulfanilamide particularly has met with favor. The powder has been instilled into tooth sockets, periapical abscesses and used following operative procedures. Adams[79] has devised a saturated solution to be used as a hot irrigation. Whereas at body temperature a solution of ½ of 1 per cent is possible, at 60 C a solution of about 6 per cent can be made. This heated solution when cooled to body temperature upon injection theoretically allows 5½ per cent to be precipitated and left deposited in crystalline form in the infected area.

In certain cancerous areas, such as cancer of the rectum where secondary infection is quite common, sulfanilamide and particularly sulfathiazole have been found to be quite helpful in decreasing the infection and consequently in alleviating pain and suffering. On lesions about the penis, such as Ducrey infections and herpes, the local application of sulfathiazole has resulted in prompt response with alleviation of symptoms in 3 to 4 days. Manion and Allen have claimed good results by placing the powder of sulfathiazole in the bath soap used in the nursery, thereby eliminating impetigo. When applied locally to weeping lesions good results were obtained in 48 hours.

Certain toxic effects may result from the local application of the powder or solutions of these various compounds. If enough is absorbed to give a high blood level of the drug, the same toxic manifestations may occur as with oral or parenteral administration. Toxic reactions in hypersensitive individuals have been seen and may result from usual therapeutic doses described for this method. In his work with fractures and osteomyelitis Key has noted that sulfanilamide implanted locally sometimes gives rise to an unexplained elevation of temperature after operation. He adds that sulfathiazole is more apt to do this than sulfanilamide. With the British Expeditionary Force in France it was noted that certain individuals who had local application of powdered sulfanilamide developed a local cold odorless abscess. The drug in these in-

eschar After 10 days compresses of the above mixture were applied For ambulatory patients the wounds were cleansed first Then an ointment of 5 per cent sulfadiazine in 8 per cent triethanolamine in a stearin base was applied and repeated in 24 and 48 hours The author observed no infections resulting in 114 of these cases and felt that up to the present time this method was the best treatment for burns In experiments he demonstrated that the triethanolamine was not toxic If skin grafts are to be applied later it has been found that when grafts are applied to a clean surface a better take is obtained if no powder is used for several days Should the same organism recur in the wound it will respond usually to more powder applied later The administration of the drug by mouth as well as locally may be helpful

The local use of sulfanilamide *intraperitoneally* is receiving widespread interest The chief indications for its use have been in operations upon the appendix with associated intraperitoneal suppuration and in operations upon the small bowel with suppuration In 268 cases of appendicitis of which 201 were simple acute appendicitis 23 with abscess and 44 with peritonitis Mueller applied 2 to 8 grams of sulfanilamide intraperitoneally placing $^2/_3$ of the total amount in the peritoneum and $^1/_3$ in the wound there was no mortality Such doses give a local concentration of the drug from 75 to 100 times greater than occurs in the blood stream Clinically as well as experimentally it has been observed that if large doses such as 15 to 16 gm are applied a severe toxic hepatitis with jaundice results from absorption into the portal circulation and its direct transportation to the liver for detoxification It has been advised that if sulfanilamide is used locally the peritoneal cavity is not to be drained

The absorption of these various drugs from the peritoneum is extremely variable In some interesting toxic experiments on guinea pigs carried out by Throckmorton [78] in giving intraperitoneal doses of 1 gm per kilogram body weight of sulfanilamide sulfapyridine sulfathiazole sulfadiazine sulfamethyldiazine and sulfaguanidine this author found sulfanilamide to be innocuous Sulfapyridine because of its lesser solubility was the most toxic giving rise to tissue edema and a foreign body giant cell reaction All the other compounds were only slightly or negligibly reactive Several observers have cautioned against any local application of the sodium salts particularly *sodium sulfapyridine* and *sodium sulfathiazole* because of their very irritating qualities

In the short interval since its introduction already sulfanilamide powder has been applied locally under numerous and diverse circumstances from plastic surgery to athlete s foot (epidermophytosis) It is

even being tried as a snuff for head colds and upper respiratory infections but without much success Only a few of these will be discussed The powder has been applied in the wounds of herniorrhaphies with rapid healing without infection and with retention of apparently normal tensile strength of the scar Studies of its application to the brain in neuro surgery have shown this to be a safe procedure At first it may cause a slight focal meningeal leukocytic response which disappears promptly Microscopically some crystal particles may remain which become encased by foam cells Absorption of the drug is quite rapid and by comparison it seems to cause less tissue reaction than silk or silver clips

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stances failed to lower the temperature to normal These lesions were looked upon as complications of the treatment and were termed sulfanilamide abscesses Drainage of them usually brought about a prompt recovery

The Local Use of Sulfadiazine

The use of sulfadiazine by local application has received considerable study, but there exists also considerable controversy as to its proper place, the best methods of application and the evaluation of end results As has been pointed out in previous sections of this chapter many of the profession have tended to discard previous sulfonamide compounds and the knowledge accumulated with their use, for any new derivative that makes its appearance and have had the expectation that the new compound will do all that previous ones are known to do plus more in addition The result has been a tremendous enthusiasm with the launching of each new derivative that had to be tempered with time and the acquisition of experience These remarks are in a preliminary way to the statement that although many observers have recommended sulfadiazine as the drug of choice for local application we are still a good distance from the final answer As with the other sulfonamide compounds the probability is that eventually each will find its proper place and application and sulfadiazine will be among them From what is known of this drug it seems fair to continue to treat certain conditions with it by local application but not to discard the proved value of local application of some of the others, particularly sulfanilamide and sulfathiazole There is already an inclination in that direction and some of these trends will be brought out in the following discussion

The local application of sulfadiazine has been used chiefly in the treatment of war wounds burns in connection with operations in the peritoneal cavity and the skull, in certain diseases of the eye and a few dermatological conditions As has been brought out already in this section the value of local application of any of these compounds, including sulfadiazine, lies in the concentration that can be attained locally to exert a bacteriostatic and/or a bactericidal effect and at the same time will not be harmful to the tissues of the host Concentration at least in part, is dependent upon solubility and we have seen that sulfanilamide sulfaguanidine and sulfathiazole are all more soluble than sulfadiazine at body temperatures In using powdered forms of the various sulfonamide compounds in bone marrow cultures of bacteria Osgood[38] found sulfathiazole more effective over a greater range of organisms but the effectiveness of sulfadiazine was satisfactory When sulfadiazine is placed in a glycerine base paste in 5 per cent strength, it seems more effective for local application but tends to cause allergic reactions It is safer to apply it in a petrolatum base in water or as a powder

Like sulfanilamide sulfadiazine offers the advantages of slow absorption with a minimum tendency to clumping with resulting foreign body reactions Sulfathiazole and sulfapyridine tend to be slightly more irritating to tissues locally Some recent studies have suggested that the local bacteriostatic effect of sulfadiazine may be enhanced by the additional application of urea[386] and hydrogen peroxide[387], preventing contamination and insuring activity thereby adding to the factor of safety The addition of urea to a sulfonamide applied locally tends to eliminate the effectiveness of p aminobenzoic acid and methionine in preventing sulfonamide action Fox[0] has advocated the use of sodium sulfadiazine locally on the basis that it is only slightly ionized This relative acidity of sulfadiazine suggested to him that its low water solubility could be increased in a physiological buffer in which it would exist in larger proportions as the extremely soluble ionized sodium salt In dogs Fox found that sodium sulfadiazine in high concentration caused little irritation to the tissues and that following intramuscular or intraperitoneal implantation the drug was transferred continuously from the site of implantation to the general circulation over 24 to 48 hours On the other hand Gundrum[395] using an aqueous solution of sodium sulfadiazine with a pH of 9 87 and buffering it to a pH of 4 7 found that 10 drops instilled into the nostrils of rabbits three times a day for 30 days caused considerable local damage Sections of the nose showed inflammation throughout thickened mucous membrane patchy degeneration of epithelial layers and some necrosis and sloughing of the soft tissues There was no injury to bone or cartilage From this study Gundrum concluded that while not so completely destructive as sodium sulfathiazole sodium sulfadiazine was definitely injurious

Further in the consideration of the local application of sulfadiazine the reaction of the tissues seems to play an important part On the basis that infected wounds are acid that the sulfonamides are ampholytes within certain limits and that increasing the alkalinity of the local tissue reaction increases sulfonamide dissociation thereby increasing the effectiveness of the molecular form Schmelkes[405] has given reasons why alkalies locally with the drug may produce more rapid wound healing He recommends calcium carbonate because it acts not only as a buffer but also as a reservoir of buffer and from the fact that calcium ions stimulate phagocytic activity The fact that calcium carbonate is insoluble seems to play little part in this connection since he claims that it becomes soluble to the extent that acid is produced in the wound and that its buffering ability is called into play In clinical application some favorable results are being reported with such a combination The final answer to such applications will depend upon further studies and experience

Concerning the benefits derived from the local application of the sulfonamide compounds in the treatment of *war wounds* there is no doubt The present status

tics suggest that at least 50 per cent of deaths from infectious diseases and battle wounds in World War I might have been avoided if the sulfonamides had been available at that time Several competent observers have placed sulfonamide treatment among the first three most important measures in the therapy of battle casualties Major Ascroft of the Royal Army Medical Corps asks "what are the real essentials of immediate po toperative treatment in 9 out of 10 battle casualties? " and answers the question by saying "they are food and drink, warmth and rest and sulfonamides "[389] Surgeon General Kirk names plasma, surgery and sulfa drugs, in that order in giving credit for most of the recent reduction in mortalities[390] This applies, of course to both the local and systemic application of these drugs A study of the bacteriology of war wounds has shown[391] that the infecting organisms most frequently are fecal and pyrogenic, such as enterobacilli enterococci, clostridia staphylococci and aerobic and anaerobic streptococci Sulfadiazine is effective against most of these But it should be remembered that *the local and general use of the sulfonamides in civil practice as well as in war* should be as a therapeutic adjunct to careful debridement and definitive surgery However, the situation that obtains in war casualties may be quite different from casualties of civilian life In civil life definitive surgical treatment probably will be given promptly and in most instances the administration of a sulfonamide such as sulfadiazine can be deferred safely until just prior to or after the definitive treatment In battle casualties on the other hand the persons wounded may not have had access to bathing facilities for days even weeks, they may have become covered with dirt and debris, and definitive surgical treatment may have to be delayed for some hours This situation has led to the combined oral and local use of the sulfonamide compounds both prophylactically and therapeutically The best results seem to be obtained by the use of sulfanilamide powder locally and sulfadiazine by mouth as advocated by Long[39] Sulfanilamide in doses of 3 to 5 0 gm in powder form is preferred for local administration because of its greater solubility its lack of tissue reaction and its effectiveness against the organisms usually encountered Sulfadiazine is preferred by mouth because of its ability to be retained in the circulating blood stream with the maintenance of an effective blood level When used prophylactically in battle casualties the initial peroral *dose of sulfadiazine should be 4 0 gm (gr 60) given as soon* as possible Since the soldier may be dehydrated, and since experience so far in World War II has demonstrated an excellent evacuating program for the sick and wounded it is advisable to recommend that no more of the drug be taken after the initial dose until definitive surgery has been carried out and the medication can be controlled At that stage 1 0 gm (gr 15) may be administered every 4 to 6 hours, day and night, for a period of 7 to 10 days If infection occurs in spite of this treatment, the drug may be continued as indicated, being careful to observe fluid balan e

If the wound is a closed one the combination of sulfanilamide powder locally and sulfadiazine by mouth will give a blood concentration varying from 8 to 15 mgm per 100 c c in the first 24 hours if the wound is an open one, the concentration will be somewhat less 5 to 10 mgm per 100 c c In a report of a study made for the State of New York[3] by a special committee on fractures much the same principle is advocated i e sulfanilamide locally after debridement and sulfadiazine by mouth with the addition of antitetanus serum or tetanus toxoid in compound fractures In attempting to outline uniform procedures for the armed forces in the prevention of infection in wounds and burns the National Research Council advises sulfanilamide preoperatively 5 0 gm implanted locally and 1 0 gm (gr 15) every four hours by mouth [9] Postoperatively it is advised to use sulfadiazine by mouth 1 0 gm (gr 15) every 6 hours day and night for 7 days With either method the important thing for systemic effect is the maintenance of an adequate blood level using whichever drug is the most effective against the particular organism encountered taking into consideration the possible toxic effects

Whereas previously sulfanilamide had been advocated in the treatment of penetrating abdominal wounds which lead to perforation of hollow viscera sodium sulfadiazine parenterally has been recommended recently [9]

In the local application of sulfadiazine probably its use in the *treatment of burns* has received the greatest attention Following the introduction of tannic acid therapy for burns 1925 the mortality fell from approximately 35 per cent to 12 per cent With the introduction of the sulfonamides along with the other measures the mortality now is said to be between 3 and 5 per cent Such figures however will vary with the circumstances for the extent depth secondary infection burns on the battlefield and promptness of treatment of the burn have a bearing on the end result

In the past several years a great deal has been written on the treatment of burns that has attempted to formulate and to clarify certain basic principles Although there remain some differences of opinion in certain details all of the studies have pointed out that the proper treatment and after care of a burn consists of more than simply the application of some substance to the involved area These features are stressed here briefly because for any burns of more than minor degree they are of much more importance than the local application of tannic acid or a sulfonamide compound These other measures consist of proper cleansing of the wound with a cloth or soft brush soap and water and debridement under anesthesia if necessary the treatment of primary and secondary shock when they exist using hematocrit determinations rather than blood pressure readings in following the clinical course of the patient and supplying red blood cells as well as sufficient plasma to restore circulating blood volume and adequate

oxygenation of tissues The final phase of treatment includes all of the attempts at complete rehabilitation of the patient with plastic surgery, physical therapy and occupational therapy used as seems necessary Since every burn of significant extent must be considered to be potentially infected, this is the place where the sulfonamides may be able to play a part There is ample evidence that *sulfadiazine* is a useful chemical in the treatment of burns, but whether it is always the method of choice under all circumstances has been debated It has been accepted by the National Research Council and directed to the Armed Forces as the drug of choice in the treatment of all burns[396] It may be used locally and/or parenterally

The recommendation of the War Department is its use by mouth as a prophylactic in all cases with moderate to severe burns Its use by mouth is recommended because blood levels of the drug can be best controlled in this way, when used locally with its erratic absorption from burned surfaces blood levels cannot be controlled The initial dose is 4 0 gm (gr 60) with no more to be given except under the direction of a physician because of the fluid loss and kidney damage so common in burn cases Where it seems urgently needed a maintenance dose of 0 5 gm (gr 7½) may be given every four hours until adequate kidney function can be demonstrated and fluid balance has been established Then the dosage may be increased to 1 0 gm (gr 15) every 4 hours The sodium salt may be used intravenously for prophylaxis and treatment although in air raid and military burns there may be little chance of intravenous therapy In civil life however intravenous sodium sulfadiazine may be of help as carried out in the management of the victims of the Cocoanut Grove disaster in Boston in 1942 The intravenous use of the drug was carried out because many of the patients were unable to swallow Thirty nine cases from that catastrophe were treated at the Massachusetts General Hospital by the routine administration of 2 0 gm (gr 30) of sodium sulfadiazine in 40 c c of distilled water injected into the rubber tubing of each set for intravenous therapy[397] Subsequently each patient was given 2 0 gm (gr 30) twice a day by the same route When it could be taken orally sulfadiazine was given in doses of 1 0 gm (gr 15) every 6 hours The mortality rate in this series was nearly 18 per cent With the remarkable efficiency with which this hospital met the emergency it is only fair to state that there was little filth or dirt as one would find in battle and evacuation to the hospital took place within 15 to 30 minutes Various types of organisms persisted in the wound, although sterile boric acid ointment strips had been applied locally, and the blood level of sulfadiazine in many cases seemed adequate with the parenteral therapy Streptococci however remained present in only two cases Finally the deaths were not due to secondary infection but to a diffuse membranous bronchitis from toxic fumes and in 1 case suicide So

the true benefit of sulfadiazine therapy in this series is somewhat difficult to evaluate

The intravenous or oral therapy of burns with sulfadiazine is a reasonable approach along with other measures mentioned since there is general agreement that sepsis is the most common cause of death in extensive burns where the patient survives primary and secondary shock and hepatorenal damage This view is reasonable, for streptococci have been found in the blood stream following severe burns [3] Furthermore after systemic administration of sulfadiazine fluid aspirated from an unruptured bleb resulting from a burn will be found to *contain appreciable amounts of the drug This ability of sulfadiazine to penetrate* into blister fluid plus the protection afforded by the epithelium of the bleb are two very important factors which make for better results in the treatment of burns when the blebs are not ruptured

It is to be pointed out that whether given parenterally or locally the sulfonamides are to be used more cautiously in the treatment of peace than of war casualties For in civil life one is dealing with all age groups many with preexisting disease *whereas with the military the vast majority have been previously healthy* In older civilians the toxic effects are greatly enhanced So a delay in their use is permissible in civilians for hospitalization usually is available quickly, in war casualties hospitalization may be delayed for hours

The use of sulfadiazine by local application for the treatment of burns may be said to have begun with the report of Pickrell He used a mixture of 3 per cent sulfadiazine in 8 per cent triethanolamine sprayed from an atomizer In the treatment of 100 ambulatory and 15 hospitalized cases only one showed any evidence of infection The procedure is to spray the wound every hour the first day every two hours the second day every three hours the third day and every four hours the fourth day Pickrell s solution has a pH of 8 7 to 9 0 It is clear with a faint yellow color owing to the oxidation of the sulfadiazine Although this discoloration does not seem to affect materially the efficacy of the drug it may be prevented by storing it in a dark glass bottle The solution is odorless has a somewhat bitter taste and does not stain skin or clothing

It forms a transparent crust which may cause a burning pain at the time of first application but thereafter the pain is relieved quickly It penetrates somewhat into the tissues depending upon the extent and depth of the burn and can be detected in the blood within several hours after being sprayed on a wound After the eschar forms for like tannic acid and other protein precipitants Pickrell s solution is an escharotic the blood level approaches a minimum and tends to remain level Normal tissue is little affected by the drug In one series of 50[4] and another series of 32 patients this method of treatment seemed satisfactory to the authors although attempts to vary it and modify it are constantly

being presented It may be said to have distinct advantages, however, such as its use about the face, hands or genitalia, its comfort to the patient, its ability to inhibit infection its flexibility which allows patients to turn and to move about its transparency and lack of staining qualities Yet not a few criticisms have been directed against it The most prominent is the time consumed in obtaining an eschar The editor of the British Lancet[403] has voiced the opinion of many in saying an eschar may take as long as 4 days to form and during that time as many as 50 separate sprayings must be carried out During the whole of this time the moist surface must be protected from cross infection and this, together with the obvious difficulties of spraying a circumferential burn, may well be beyond the resources of a hard worked hospital or field unit in periods of emergency Meyer and Gradman[404] point out the frequency with which the eschars tend to crack and curl at the edges leaving a portal of entry for infection Serum tends to accumulate beneath the eschar unless a pressure bandage, preferably light mesh gauze and mechanic s waste[395], is applied Furthermore eschars do some damage to epithelial cells with protein coagulation and tendency to adherence In this connection Schmelkes[405] has pointed out that strongly alkaline solutions of sulfadiazine cause some damage to surface epithelium Pickrell s solution has pH 9 0 On large surfaces toxic reactions are possible from absorption Finally Colebrook and others in work quoted by Brown and McDowell[398] feel that the sulfonamides should not be continued locally over a long period because of giant cell formation and slowing of healing If not used carefully and properly, subsequent skin grafting may be impeded

Some of these criticisms have been carried further in studies in which the Pickrell spray treatment has been compared with other methods In the therapy of 43 cases of burns Thiessen and Steinreich [47] applied the sulfadiazine triethanolamine spray to 12 gentian violet to 18 5 per cent tannic acid to 4 and cod liver oil ointment to 9 cases The burned areas involved 5 to 9 5 per cent of the body surface and on the basis of days required in hospital cod liver oil was best (9 4 days) gentian violet second (17 3 days) tannic acid third (21 0 days) and sulfadiazine last (28 3 days) The authors conclude that " the results from this treatment (sulfadiazine) on the whole were no better and no worse than with other agents of this general type As a matter of interest their best results were obtained in several cases in which they used sulfathiazole incorporated in cod liver oil ointment Meyer and Gradman[404] treated 10 cases by applying Pickrell s solution to certain burn areas using Koch s pressure dressings of xeroform in other areas as controls and found 23 per cent infection in the spray treated areas as compared with 7 per cent with the xeroform dressings The incidence of good healing with spray treatment was 50 per cent and with xeroform 80 per cent In spite of these various criticisms which can be well taken the application of

sulfadiazine locally in the treatment of burns when done carefully seems to have a definite place

The study of Meyer and Gradman[4 1] recalls another factor in the treatment of burns that warrants brief discussion It is the open versus the closed method of therapy By open is meant reversible methods of dressing such as leaving blisters intact using cotton swabs or fine mesh gauze (no 44) next to the wound and enclosing the entire area in a mechanic s waste dressing for pressure to prevent swelling and loss of serum and to produce comfort still permitting surgical drainage[194] It does not mean necessarily leaving wounds exposed and unprotected There is much to be said in favor of the open treatment of burns particularly those covering large areas and flexible surfaces and wounds that are deep It has many adherents By the closed method is meant any coagulating or tanning procedure such as tannic acid which is not a reversible process except with operative removal of the membrane The eschar formation with Pickrell s solution is such a closed method

Using the terms open and closed in this sense Pickrell [06] has introduced more recently a formula using sulfadiazine to prepare a film for use as an open surgical dressing It contains 3 per cent sulfadiazine or sulfanilamide 2 5 per cent methyl cellulose methocel 3 per cent triethanolamine and 0 5 per cent sorbitol with either 50 per cent alcohol or acetone to make 100 c c The use of acetone permits rapid drying whereas the 50 per cent alcohol requires several hours of drying at 75 C The emulsion is sprayed with a pressure gun or paint spray on a smooth horizontal glass surface The resulting film when dry is stable and can be sterilized by dry heat It is estimated to contain from 35 to 50 per cent of sulfonamide This dry open (reversible) method is used as follows The burned area is cleansed with a detergent then washed with saline sulfadiazine or azochloramide solution and while still moist the film is placed to over lap the burn edges Then a smooth firm pressure dressing of gauze is applied The film should remain in place for three to five days at which time epithelialization should be taking place At the end of this time most or all the film will have disintegrated The film may be renewed as desired

Clark and his associates[4 7] who have tried this method feel that because the film is without fabric it tears too easily when wet and dissolves too rapidly so they have proposed a synthetic escharotic bandage prepared by drying a sulfonamide methyl cellulose solution on fine meshed rayon nylon silk or veiling Their solution contains 5 0 per cent methyl cellulose 0 1 per cent aerosol 10 0 per cent triethanolamine 1 0 per cent sodium lauryl sulfate 1 0 per cent propylene glycol carbowax or sorbitol 2 0 per cent sulfadiazine or sulfathiazole 2 0 per cent urea and 0 per cent thiourea or sodium acid sulfite Such impregnated material is applied as a pressure dressing over the wound

Numerous other prescriptions containing sulfadiazine have been advocated for the local treatment of burns but the results of clinical application are not at hand. Tannic acid still seems to enjoy a rather wide reputation in the therapy of burns; hence a few have advocated the combining of tannic acid and sulfadiazine in an ointment base for local application. One of these contains pectin (N.F. VII) 5.0, tannic acid 10.0, glycerine 12.0, sulfadiazine 5.0, methyl parahydroxybenzoate 0.2, sodium sulfite 0.2 and Ringer's solution 67.6. Mix well the pectin, glycerine and sulfadiazine to a smooth paste. Dissolve the sodium sulfite, methyl parahydroxybenzoate and tannic acid in boiling Ringer's solution. Add to the pectin paste and stir well until it cools to room temperature. Such a mixture for open dressing contains 10 per cent. tannic acid and 5.0 per cent. sulfadiazine[408]

Although tannic acid has had many adherents in the treatment of burns, the more recent developments are tending to omit it. Firstly, it should not be used on the hands, face or genitalia because the eschar it produces may be sufficiently constricting to damage permanently the muscles and delicate tissues. Even more important than a constricting effect, particularly about the genitalia, is infection which is so difficult to control in this location. For such areas particularly, sulfadiazine may be used with benefit. In fact in burns about the genitalia and rectum all that may be necessary is proper washing and cleansing with mild solutions with no application of ointment or eschars. Secondly, Wells, Humphry and Coll[409] have found recently that tannic acid injected subcutaneously into rabbits produces hepatic lesions with central necrosis similar to the liver lesion found at autopsy in patients who had been treated by the tannic acid method[410]. That tannic acid may be a factor in some deaths from burns seems not to have been appreciated in the many years that this method of treatment has been in vogue. Thirdly, in some interesting experiments with mice, in which he demonstrated that excessive cooling or heating exerted an unfavorable effect on burns, Rosenthal[411] found that tannic acid as well as sodium sulfadiazine (from absorption) increased the mortality rate. Fourthly, tannic acid treatment may cause a delay in subsequent skin grafting. In relation to plastic procedures the sulfonamides such as 5.0 per cent. sulfadiazine ointment seem to be most indicated during the acute stages of the burn and then again for a few days before grafting[398]. Finally, various committees of the National Research Council have withdrawn tannic acid ointments or jellies entirely in the emergency local treatment of burns[393]. They advise (a) morphine to relieve pain, (b) covering the area with sterile boric acid ointment or petrolatum or 5.0 per cent. sulfathiazole ointment over which one or two layers of fine mesh gauze (no. 44) is smoothly applied, and (c) over this thick sterile gauze or sterile cotton waste is to be placed and the entire dressing bandaged firmly but not tightly.

The benefits to be derived from the use of sulfadiazine in the treatment of war gas burns are essentially unknown

In *surgical operations within the abdominal cavity* sulfadiazine by local im plantation has received considerable trial As brought out previously in the dis cussion of the pharmacology of this drug its absorption in man is slower than sulfanilamide or sulfathiazole It tends to produce a somewhat greater local reaction than either of the other two drugs but perhaps less than sulfapyridine The reaction it produces in the peritoneal cavity depends in part upon the amount used for small yet adequate doses (4 to 6 gm) according to Hawking and Hunt[41] produce little irritation Herrell on the other hand advises against its use en tirely[41] He prefers sulfathiazole Good results have been reported with its use however in which 4 0 gm were implanted into the peritoneal cavity and 2 0 gm into the wound at the end of the operation without untoward effects [14]

Sulfadiazine like sulfanilamide has been found to have no inhibiting effect on wound healing when adequate concentrations are maintained in the blood and when caking in the wound is prevented In their study of 2 000 surgical infec tions Veal and Klepser[41] voice the opinion of numerous investigators that in surgical procedures in general sulfanilamide locally and sulfadiazine parenterally or by mouth when infection is present is considered the most effective combina tion Key has gone so far as to advocate a sulfonamide locally in all orthopedic operative wounds whether infected or not[41] Whether that is advisable will await further trial by others Sodium sulfadiazine is too alkaline for local appli cation to mucosal or serosal surfaces

Sulfadiazine has been applied locally to the *brain* with good results and without untoward effects Ingraham and Alexander [7] favor this drug over the others because of its bacteriostatic effect on a wider variety of organisms In a study of the bacteriology of wounds of compound fractures of the skull Munro[418] found staphylococcus aureus and albus hemolytic streptococcus meningococcus and pneumococcus in that order of frequency Sulfadiazine is effective against all of these He points out further that the incidence of infection rises rapidly during the second and third days For this reason operation may be postponed up to 48 hours after the injury without added danger of infection provided debridement is complete and chemotherapy is used to inhibit further growth That sulfadiazine is not injurious to brain tissue has been shown by Hurteau By placing the various sulfonamide powders on the cerebral cortex Hurteau found sulfanilamide the most rapidly absorbed sulfathiazole next sulfadiazine third and sulfapyridine least Sulfadiazine caused no neuronal destruction when placed directly in con tact with the meninges or cerebral parenchyma There was no glial reaction and but little foreign body reaction in the meninges Sulfadiazine also exercised no unfavorable effect upon the final result of the wound healing process It is sug

gested that in a small wound of recent origin where infection has not yet had time to become well established one may well choose a sulfonamide which will be rapidly absorbed such as sulfanilamide, but if there is a chronic source of infection as in wounds communicating with the paranasal sinuses, it is logical to employ a sulfonamide that will exert its effects over a longer period such as sulfadiazine

Sulfadiazine in either 1.0 or 5.0 per cent strength has been used extensively in local applications to the *eyes* Such conditions as ulcers, blepharitis impetigo and staphylococcal conjunctivitis are said to respond well to local treatment For most forms of conjunctivitis Thygeson and Braley[40] prefer sulfathiazole For hemolytic streptococcal infections staphylococcus other than conjunctivitis pneumococcus *B pyocyaneus* and Friedlander s bacillus infections combined oral and local therapy should be used In such conditions of the eye as non hemolytic streptococcal infections tuberculosis, tularemia, Parinaud s conjunctivitis ocular pemphigus uveitis sympathetic ophthalmia and virus infections, sulfadiazine ointment locally has been found to be without effect[41] The direct application of sulfadiazine crystals has been suggested in dacryocystotomy, dacryocystorrhinostomy for empyema of the sac lacerations of the lids perforating wounds of the orbit infections of contracted sockets retrobulbar suppurations fistulas and non tuberculous osteomyelitis of the lacrymal bone If systemic therapy is advisable in addition, blood levels of sulfadiazine should be kept at 6 to 10 mgm per 100 c c

In various *skin diseases* sulfadiazine in ointment lotions or powder form has had some trial In 3.0 to 5.0 per cent strength it seems about as effective as the other sulfonamide compounds and causes a favorable result in dermatoses that respond to sulfonamide therapy It is fair to add that the best results are obtained in the eradication of secondary infections of the skin and not always of the primary lesion itself For general purposes in dermatology Miller[4] finds 5.0 per cent sulfanilamide or sulfathiazole superior to sulfadiazine

In a few *other diseases* and circumstances not already discussed the use of sulfadiazine has been studied and favorable results recorded Styron and his associates[43] reviewed the cases of 100 patients with *diabetes* to whom sulfadiazine had been administered Toxic symptoms occurred with no greater frequency than has been reported in non diabetic patients No evidence of acidosis was observed The insulin requirement was increased in 45 cases during treatment but that was possibly the result more of the infection than of the drug, for 55 cases had an actual decrease in the insulin dosage presumably as the result of control of the infection These investigators point out that chemotherapy may prevent extension of foot infections but since the foot lesion is due as much to diminished blood supply as it is to infection necessary surgery should not be delayed For the

infection of diabetic gangrene particularly if it is a mixed infection Homans advises full doses of sulfadiazine by mouth

In *Addison s disease* despite the efficacy of present methods of treatment a relatively high incidence of infections of the upper respiratory tract due to hemolytic streptococcus occurs and persists Thorn and Lewis[4] have found that sulfanilamide and sulfathiazole do not seem to be tolerated as well by patients with this disease because of toxic reactions Because sulfadiazine is less apt to cause nausea and vomiting they found it quite helpful intravenously and by mouth along with saline glucose and cortex extract in the treatment of 2 patients with Addison s disease and hemolytic streptococcal pharyngitis

In studies on *blood storage* Heath and Province[4] found sulfadiazine like sulfapyridine and sulfathiazole to exert some bacteriostatic effect in stored plasma but the results were not sufficiently significant or consistent at the concentrations tested to warrant its use on a wide scale

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PART IX

The Prophylactic Use of the Sulfonamide Compounds

The effectiveness of the sulfonamide compounds against certain bacteria made their use as prophylactic agents a logical procedure Begun at first on a small scale as a preventive against the common cold rheumatic fever meningitis and a few other diseases an exceptional situation for their trial on a large scale presented itself with the outbreak of the present war Infections and diseases frequently have caused a higher mortality in previous wars than have battle casualties Where large groups of recruits are housed together epidemics are almost certain to follow Therefore not only to prevent deaths from disease but to prevent disease from causing loss of manpower working hours would be a great economical step forward in the waste of war Then too the military command allows for controlled studies to be carried out since many factors can be regulated on a large scale in a way not possible in civilian life As the following discussion will show extensive advances have been made especially by the military in demonstrating the efficacy of the sulfonamides as prophylactic agents against certain infections

In any prophylactic trial of these drugs several questions present themselves some of which have been answered others only partially so Such questions would include (1) How large should the series be to be of statistical significance? (2) What is the optimum dosage for prophylaxis not too large because of possible toxic reactions not too small? (3) For what period of time must the drug be given to be effective? (4) Will long continued administration cause toxic reactions? (5) With drug fast strains of organisms having been produced clinically and experimentally will small prophylactic doses of the sulfonamides produce drug resistance? (6) Will small doses over a shorter or longer period of time sensitize the individual to that drug or to related compounds? (7) What percentage of individuals will develop toxic reactions and what will be the chief manifestations? These and other questions came to be answered particularly when epidemics began to occur in our military camps where these drugs were administered prophylactically not by choice but out of necessity

It has been pointed out in previous sections that the sulfonamides are ineffective in the treatment of uncomplicated acute catarrhal fever the *common cold* Later studies continue to confirm this[3 5 4] To reduce the incidence of secondary invaders however such as pneumococci streptococci staphylococci and H influenzae against all of which the sulfonamides are effective to a degree Cecil Plummer and Smillie[554] suggest that sulfadiazine may be administered as a

prophylactic during a cold, 1 0 gm (gr 15) 3 times a day for 4 or 5 days This dosage, which will give an average blood concentration of 7 0 mgm per 100 c c, has been found to reduce temporarily the pharyngeal flora and is suggested for use in selected cases, particularly those in which the history reveals an almost invariable and severe secondary infection following the cold, as asthmatic bronchitis pneumonia secondary to bronchiectasis repeated otitis media or recurrent sinusitis Kern[555] on the other hand has pointed out several dangers in the routine treatment of the common cold with the sulfonamides for in his opinion a prophylactic dose does not prevent pneumonia, it may cause drug resistance of pneumococci present, and it may prevent the proper typing of the pneumococcus The latter phenomenon has been discussed under sulfapyridine

In other *acute respiratory infections* the beneficial effects of sulfonamides given prophylactically have been demonstrated adequately The largest series and most significant observations have been carried out by the U S Army[556, 557] and the U S Navy[3, 1, 558] Sulfadiazine was used for the most part because of its known effectiveness against the streptococcus and meningococcus particularly, and because of its lesser toxicity than that of sulfanilamide sulfapyridine and sulfathiazole Several studies, including 40 large Air Force Hospitals with 25 000 beds and 800 000 troops[5, 6], another comprising several thousand troops at a U S Naval Training Station[551] and a third involving 50 camps of 8 U S Naval activities[555], have demonstrated amply that prophylactic sulfadiazine decreases both the number of sick calls and hospital admissions particularly for diseases caused by beta hemolytic streptococci These included nasopharyngitis scarlet fever and a streptococcal sequel rheumatic fever An incidental finding was a notable decrease at the same time in meningococcal, pneumococcal and gonococcal infections[559] The overall results of the benefits of sulfadiazine prophylaxis for respiratory infections in the U S Armed Forces have been given by Holbrook[556] Our army of 7 million troops spent in excess of 14 million days in the hospital last year because of common respiratory diseases In addition to this time there were the inevitable number of complications and deaths as well as additional millions of man days lost from duty If our experience with sulfadiazine prophylaxis holds true it is a conservative estimate that 50 to 75 per cent of this tremendous loss could be avoided

These various studies have shown further that a uniform dosage of sulfadiazine over a prolonged period of time is necessary for optimum benefits A dose of 3 0 gm (gr 45) once a week is ineffective Four grams (gr 60) distributed over 48 hours gives a definite but only brief reduction in the incidence of infections When 6 0 gm (gr 90) were given in 3 days the rate of hospital admissions was reduced 75 per cent but toxic reactions became somewhat more frequent A dose of 0 5 gm (gr 7½) daily will be effective in the majority of a large series but infections will continue to occur The optimum prophylactic dose of sulfadiazine for

respiratory diseases is about 1 0 gm (gr 15) daily for a period of several months To maintain a more uniform blood level which will average 2 0 mgm per 100 c c on such a dose several have advocated 0 5 gm (gr 7½) morning and night rather than the 1 0 gm in a single dose The drug should be given continuously Furthermore it appears to be just as effective when given a second season as a prophylactic or when used in larger therapeutic doses for the actual treatment of a susceptible infection Drug fastness of organisms and sensitization of the individual on such a dosage have not been observed Toxic reactions have been remarkably few less than 1 per cent, and those chiefly skin rashes These conclusions seem valid since they are based on observations of over a million men

In an outbreak of *scarlet fever* due to group A type 19 hemolytic streptococcus in which the rate of disease had risen to 10 cases a week sulfadiazine prophylactically in doses of 1 0 gm (gr 15) daily reduced the rate in one week to 4 cases a week and during the next three weeks only 5 new cases appeared[351] Here again toxic reactions were very few

For the prevention of *rheumatic fever* the evaluation of the prophylactic use of the sulfonamides is somewhat more complex In the past few years it has become appreciated that many factors are involved in the disease incidence of rheumatic fever namely heredity climate economic environment constitutional inadequacy and so on The several of these and not one alone need to be controlled in any program of rheumatic fever prevention At the same time medical opinion is crystallizing to the point of view that even though the specific cause of rheumatic fever is not known a definite relationship with streptococci seems to exist since attacks of acute rheumatic fever are preceded by hemolytic streptococcus infections in almost every instance[56] That would make the prophylactic use of the sulfonamides appear to be most valuable Yet the very nature of the disease its erratic recurrence rate would make the evaluation of such preventive treatment rather difficult unless carried out carefully over a period of a number of years or in a very large group of cases Both have been done with very gratifying results the civilian period study having been summarized by Thomas [6] and the military experience with large groups of cases by Holbrook and van Ravenswaay[56] As has been pointed out in the sections on sulfanilamide sulfathiazole and sulfadiazine these compounds exert no beneficial effects in the acute stages of rheumatic fever in fact they may be harmful But in the earlier studies [51] [8] in which sulfanilamide was used as the prophylactic agent against hemolytic streptococcal infections that precede rheumatic fever, very favorable results were obtained in that none of the treated patients developed rheumatic fever over several seasons observation whereas the incidence of the disease in the control groups amounted to 10 to 20 per cent A dose of 0 3 gm (gr 5) three times a day reduced the streptococci in throat cultures [51] and was without significant toxicity These earlier studies [8] also showed that the prophylactic effect

of the drug was beneficial only during the time that the drug was taken and that those same individuals are susceptible to streptococcal infections once the sulfonamide is removed The majority of the numerous studies that have been carried out since 1942 have utilized sulfadiazine for its known effectiveness against streptococci its maintenance level in the blood stream and its lesser toxicity In a summary of civilian experience, in which 1 0 gm (gr 15) of sulfadiazine was administered daily for 5 to 6 months for a total of 815 patient seasons over a period of 7 years only 8 had recrudescences, an incidence of less than 1 per cent[561] Among the control groups the incidence of recrudescence ranged from 10 to 35 per cent

The method of prophylactic use of sulfadiazine for the prevention of rheumatic fever is recommended by Thomas[561] as follows As soon as a patient has reached a satisfactory convalescent stage following acute rheumatic fever that is when free from arthritis fever and other symptoms on withdrawal of salicylates the prophylactic sulfonamide either sulfanilamide or sulfadiazine should be started It does not appear to be necessary to wait until the blood sedimentation rate is normal Further, it seems desirable to start the prophylactic treatment before the patient returns to the home environment in order to avoid reinvasion of the nasopharynx by the beta hemolytic streptococcus For the prevention of toxic reactions it is suggested that most patients be started on 0 5 gm (gr $7\frac{1}{2}$) a day for the first 3 weeks then continue to take 1 0 gm (gr 15) a day ' day in and day out summer and winter, year in and year out, for at least 5 years and probably longer in younger children if the patient is to be safely steered through the period when recrudescences are most frequent [561] This method appears to be very effective in a long range program However, if the drug is started during a latent period after the streptococcal infection has occurred but before the appearance of the acute rheumatic fever, the streptococcal infection can be brought under control, but the acute rheumatic attack will develop regardless of the medication It has been advised further that prophylactic sulfonamides be given to rheumatic subjects during tooth extraction or tonsillectomy In an attempt to compare the benefits of the removal of rheumatic patients to a warm climate of low incidence with the benefits from prophylactic sulfonamides Boyer[35] has felt that it is better for the patient to remain in the north and receive sulfonamide prophylaxis than to move south and receive no prophylaxis

A contrasting type of study, utilizing large groups, as summarized by Holbrook[558, 562], has been carried out in the U S Armed Forces, Army, Navy and Air Corps Although specific figures, as they pertain to rheumatic fever, are not available in the published reports they have resulted in an enthusiastic opinion that the prophylactic use of sulfadiazine in the control of upper respiratory infections has decreased distinctly and appreciably the incidence of rheumatic

fever. Instead of choosing either sulfa prophylaxis or southern climate the U.S. Army Air Corps has done both, thereby improving its results.

Except for the single series reported by Stowell and Button[563] in which toxic reactions were as high as 37 per cent, all the others report a very low incidence of untoward effects from the drugs, 0.3 to 2.0 per cent, when used prophylactically, and the majority of these are very mild, with slight fever, skin rashes and occasionally leukopenia. It has been pointed out that the latter manifestation may not appear until after the drug has been taken for 75 to 100 days and that it may recur when the drug is used a second season[564]. Any anemia that may appear as the result of the drug usually will respond to ferrous sulfate. Individual sensitization and drug fast strains of organisms have not been observed. It may be pointed out, however, that drug sensitization may take some time to develop, a factor which has not always been considered in these studies.

Before the present war sulfapyridine had been tried prophylactically in a few instances against *meningococcus infections* with promising success[93, 294, 295]. Since 1942 most of the studies have been concerned with the use of sulfadiazine with its known effectiveness against this organism, but their methods of use and dosage have been somewhat different from their use against acute respiratory infections and rheumatic fever. For a higher dosage seems necessary to attain the results and therefore a shorter time of administration if toxic effects are to be avoided. Experiments in a U.S. Army laboratory have shown that the peroral administration of 3.0 gm. (gr. 45) of sulfadiazine daily for 3 days rapidly eliminated meningococci from the nasopharynx, the throats remaining negative for as long as 8 weeks[565]. Other studies have shown that it requires at least 2.0 gm. for parasitic cure, but the length of resultant negative interval with this dose may not extend beyond 14 days[566]. Furthermore, such chemoprophylaxis as has been used against the meningococcus does not control the incidence of reinfections indefinitely, nor does it confer freedom from, or enhance resistance to, subsequent infection over any long period of time. However, when the carrier rate of meningococci exceeds 20 per cent, considered by some to be epidemic proportions (average in recruits 1 to 2 per cent, normal for the general population 4 to 6 per cent), sulfadiazine has been found to be extremely effective in reducing promptly the incidence of carriers and subsequently the cases of meningococcemia and meningitis. Since meningitis is the dreaded end result of infection with the meningococcus, the actual treatment of meningococcemia as an isolated entity may be considered prophylactic therapy against meningitis.

Two of the earlier studies with sulfadiazine as a prophylactic against the meningococcus which have been mentioned under the clinical uses of sulfadiazine[379, 548] paved the way for further trial. Beginning with 1,000 naval personnel with a carrier rate of 57.6 per cent, Cheever[548] gave 8.0 gm. (gr. 120) over 72 hours to 161 carriers and obtained clearance of the organism from the

nasopharynx in every instance The same investigator extended these studies to include approximately 600 000 men but altered the dose to 0 5 to 1 0 gm (gr 7½ to 15) a day for 7 weeks with a reduction of meningococcus meningitis to practically nil Kuhns and his associates[5~] studied meningococcic epidemics at two camps varying the dosage of sulfadiazine and using adequate controls In camp A they gave 8 000 men 1 0 gm (gr 15) three times a day for 3 days and no more There were 9 300 in the control group During an 8-week period of observation no cases in the treated group developed meningitis 23 in the control group came down with the disease In camp B they tried smaller doses giving 7 000 men 1 0 gm (gr 15) twice a day for only 2 days Here there were 9 500 as controls Again, during 8 weeks observation 2 cases in the treated group 17 in the controls developed meningitis The carrier rates were reduced from 36 and 30 per cent to 5 4 and 0 0 per cent in the 9 0 gm and 4 0 gm groups respectively The group receiving the larger doses did have a slightly higher incidence of toxic reactions In the final analysis the 4 0 gm in two days seemed nearly as effective as the 9 0 gm in 3 days Lewis and his associates[567] gave smaller doses over a longer period 2 0 gm (gr 30) a day for 2 days then 1 0 gm (gr 15) a day for 2 days more and Painton[568] gave more concentrated dosage 5 0 gm (gr 75) in 18 hours both reported good results At the present time the most satisfactory prophylactic dosage to reduce the carrier rate, to practically eliminate the occurrence of meningitis and to keep the number and severity of toxic reactions at a minimum appears to be 1 0 gm (gr 15) 2 or 3 times a day for 3 days[569]

The prophylactic use of the sulfonamides against *gonococcal infections* particularly gonorrheal urethritis in the male has been an interesting one and not so easy to evaluate When carried out on a large scale it has been criticized that promiscuity is being encouraged This prejudice has been overcome in some series by giving the drug after the sexual exposure has taken place rather than before This raises the question How long after exposure is the drug effective in preventing gonorrhea? And again how large a dose is necessary? Need a second dose be given? In the evaluation of gonorrheal prophylaxis with the sulfonamides much depends upon the history of the patient The integrity of the sexually promiscuous individual usually is doubtful alcoholic intoxication frequently adds to the deceptiveness but taking all of these factors into consideration sulfathiazole or sulfadiazine parenterally or locally have appeared to be satisfactory prophylactic agents against this disease

The earlier studies on a large scale were concerned chiefly with the local application of some form of a sulfonamide into the urethra In experiments along this line carried out early in 1942 by the U S Navy Taylor[570] made up packets containing mercury oxycyanide 0 10 sulfathiazole 5 0 gum tragacanth 2 0 and distilled water to 100 0 Five c c of such an emulsion are instilled into the urethra

and held in place for 5 minutes An adequate amount also is rubbed over the foreskin sc otum and thighs In 570 such prophylactic treatments given shortly after exposure no cases developed gonorrhea syphilis chancroid or lymphogranuloma venereum provided it had been used within 2 hours after contact A year later Blute[571] using the same formula on 80 cases aboard ship found none developing gonorrhea He points out however that if the solution is held in place longer than 5 minutes a severe chemical urethritis may result which is best relieved by the intraurethral instillation of petroleum oil 2 or 3 times a day To enhance the efficacy of mercury prophylaxis Kaufman and Litterer[572] incorporated sulfathiazole into mild mercurous chloride ointment and instilled it intraurethrally leaving it in place for several hours The ointment was made up of sulfathiazole powder 4 0 mercurous chloride mild 8 0 anhydrous wool fat 8 0 and white petrolatum 8 0 Preliminary studies on 100 men showed this formula to be non irritating to the urethral mucous membrane When applied prophylactically after contact in 2 016 instances many of whom had been exposed to known prostitutes there were only 2 failures Again these two individuals had not reported for treatment within 2 hours after exposure While these promising results were being reported the U S Army conducted field trials with single tube individual chemical prophylactic packets The most satisfactory of several formulae contained 30 per cent calomel and 15 per cent sulfathiazole (micronized) incorporated in a special vanishing cream type of base The method of use is to instruct the individual to urinate then wash the genitalia with soap and water and inject into the urethra ¼ of the 5 0 gm tube of ointment then massage the remainder of the ointment into the skin of the penis scrotum and surrounding areas No protective covering of the genitalia is needed since the ointment rubs in well and does not soil under-clothing The first field trials including 6 732 individual prophylactics resulted in 9 failures 3 individuals developing syphilis 6 gonorrhea This is a failure rate of 0 13 per cent which compares favorably with other methods of chemical prophylaxis In several thousand persons observed there was no evidence of local or systemic reaction[5 3]

The peroral administration of a sulfonamide prophylactically against gonorrhea has seemed to prove just as effective and in many instances appears to be preferred to intraurethral instillations for it is easier to carry out Further with the systemic administration there appears to be a longer period after contact during which the drug still is effective Sulfathiazole has been used the most probably because it is cheaper than sulfadiazine and therefore has been given some preference in connection with gonorrhea in the U S Armed Forces Sulfadiazine appears to be very effective also In one small series 40 marines all of whom had been exposed to prostitutes without precaution 1 0 gm (gr 15) of sulfathiazole 3 times a day for 3 days prevented the development of any gonorrhea[574] Later studies have shown that smaller doses over a shorter period of

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cent and 10 per cent sulfathiazole ointment locally afforded prophylaxis in 53 and 80 per cent respectively of autoinoculations The U S Navy routine of soap and water and calomel ointment against chancroid has not always been effective so Zeve and Schneierson[580] tried a mixture of one third of 5 or 10 per cent sulfanilamide or sulfathiazole and two thirds calomel ointment locally to 10 368 men and only 2 developed chancroid This method appears to be very effective in the prevention of such genital lesions

In the section on clinical uses of sulfaguanidine the use of that drug has been discussed in the treatment of the *typhoid carrier state* Such an application of sulfaguanidine or sulfasuccidine (succinylsulfathiazole) may be considered a prophylactic use in the epidemiology of typhoid fever in a community or an institution As pointed out the results are variable apparently more beneficial when large doses such as 20 0 gm daily are used[11] There may be little effect in the bacillary excretion in the stool however[581]

In *bacillary dysentery* on the other hand these drugs seem to be quite effective not only in checking an endemic but in the successful treatment of the carrier state In several institutional outbreaks of dysentery particularly due to the Sonne type of bacillus 0 5 gm (gr 7½) three times a day for a week or so to contacts has checked the spread of the infection and prevented new cases from developing[507, 582] In Scott s series in an institution with 3 to 8 year old mentally defective children the prophylactic administration of sulfaguanidine to 31 children and to 19 attendants appeared to be a perfect success[507] He gave the 1 5 gm dose daily to all persons regardless of age and within 48 hours the last case appeared in a child and there were no further instances of the disease The prophylactic dose was given for 6 days and 10 days and 3 weeks later all stool cultures remained negative This is in agreement with Hoagland s[583] recommendation of the importance of following up stool examinations for a sufficiently long period of time On the other hand when the drug is used for treatment of the dysentery and is stopped very soon when the symptoms subside sulfaguanidine may fail to reduce the length of the carrier state when compared with patients with Sonne dysentery not treated with this drug[584] More prolonged administration will rid the bowel of organisms

In the prophylaxis of *dental surgery* Helbraun[585] has pointed out that for the control of postoperative pain and infection in cases of slight trauma the local application of sulfathiazole into the tooth socket is no better than saline mouth washes and aspirin The rate of healing is about the same Under conditions of excess trauma however local sulfathiazole reduces decidedly the amount of discomfort and greatly hastens the healing of tissues

The use of the sulfonamides both locally and parenterally in the prophylaxis against infection in *surgical operations war wounds* and *burns* has been discussed previously in the sections on sulfanilamide sulfapyridine sulfathiazole and

time are effective also. When 3.0 gm. (gr. 45) of sulfathiazole was given by mouth during the first two hours after sexual exposure to 1,482 individuals, there was only one patient who developed gonorrhea.[575] These authors felt that such prophylaxis apparently is effective up to 12 hours after contact. Sulfonamides may be effective even when given later for Shifrin[576] found no cases of gonorrhea to develop in several thousand men when given two doses of 1.5 gm. (gr. 22½) of sulfathiazole on the day after exposure to venereal disease. Smaller doses than this however do not protect adequately. Keet[577] gave 1.0 gm. (gr. 15) doses of sulfathiazole orally after each of 1,80? exposures, and 15 men developed gonorrhea and 1 syphilis. Such a result allowed the author to observe that sulfathiazole seemed to have no affect on the incubation period of the disease.

In all of these studies the medication was given only after the sexual contact. In a very large series reported by Gooch and Gorby[578] an analysis of 5,902 exposures oral sulfathiazole was given according to 3 different plans. In the first method the man was given 2.0 gm. (gr. 30) as he left his station and 2.0 gm. upon return. In plan number 2 no sulfathiazole was given upon departure but ?.0 gm. was given upon return repeating the same dose 4 to 6 hours later. Plan number 3 was identical with plan number 2 except the dose of sulfathiazole was 1.0 gm. (gr. 15). The overall ineffectiveness by these measures was 0.172 per cent, the 2.0 gm. dosage being just as effective as the 4.0 gm. The best results were obtained when the drug was taken within 24 hours after exposure; a few escaped gonorrhea even after a 72 hour lapse of time. The taking of sulfathiazole before exposure did not appear to be of additional benefit.

The evidence seems to indicate that the sulfonamides, particularly sulfathiazole, are effective prophylactic agents in gonorrhea, whether given locally or systemically. The local administration appears to be advantageous in one respect in that when incorporated with mercury it probably prevents syphilis also in some cases. Otherwise the systemic method seems preferable for it is effective, when given as long as 24 to 48 hours after exposure, and is so much easier to administer. A dose of 2.0 gm. (gr. 30) as soon after exposure as possible with 2.0 gm. 4 hours later or 1.0 gm. 4 hours and again 8 hours later is sufficient. It is not without failure however.

As repeatedly pointed out in previous sections the sulfonamides alone are totally ineffective in the treatment of *syphilis*. Likewise they have no prophylactic value against this disease.

In the prophylaxis of experimental *chancroid* Combes and Canizares[579] gave an initial dose of 2.0 gm. of sulfathiazole orally followed by 1.0 gm. every 4 hours to a total of 5.0 gm. (gr. 75) to 5 patients whom they had inoculated. This method prevented the development of ulcers in all 5. Of various local methods tried, washing with soap, the application of calomel, mild mercurous ointment or sulfanilamide powder failed to prevent the development of chancroid. Five per

but bacteria are present in all the wounds[590] The best results appear to be obtained when the wound is left open when the pack is not too tight when skin is not removed and when the plaster cast is applied over padding and then split to allow for swelling Such patients present a real problem for the persistent infection often is resistant to later sulfonamide therapy and some of the individuals are sensitive to one or several of the sulfonamide compounds In Lyons consideration of the subject he feels that in a sense these cases represent failure to achieve a clinical objective but it would be mischievously opinionative to conclude that such end results were instances of sulfonamide failure to prevent infection At the present time many military surgeons still use local sulfonamide therapy and the majority endorse systemic prophylactic treatment

With the problem of *penetrating wounds of the chest* sulfonamide prophylaxis has been advocated by some for the prevention of pneumonia According to the experiences of Nicholson and Scadding[591] there is no evidence that pneumococcal pneumonia is more frequent after chest wounds than with other wounds They do not consider such sulfonamide prophylaxis necessary

Zinninger outlines the use of sulfanilamide powder dusted into the peritoneal cavity 5 0 gm or more to give a blood level of 8 to 10 mgm per 100 c c to obtain the best results in *penetrating wounds of the abdomen*[592] In his experience intraperitoneal sulfanilamide gives more favorable results in the contaminated peritoneal cavity than when frank peritonitis exists and such is the situation most commonly present when a foreign body has entered the abdomen It is to be understood of course that the sulfanilamide powder is applied just before the abdomen is closed after the wound has been cleaned out and the necessary surgery performed

In clean *wounds of the head* the local use of sulfanilamide after neurosurgery should not be necessary On the other hand if it is anticipated that there may be considerable delay before closure can be accomplished dusting of the wound with sulfanilamide would seem to be a wise procedure[593] In gunshot wounds of the head even if sulfanilamide has been applied locally and systemically if a long period of time such as 2 to 3 weeks occurs before definitive surgery is carried out localized gross infection is apt to be present In 10 of 12 major wounds of the head under such circumstances Carmody[594] found delay in the progress of infection but all 10 had osteomyelitis 1 a cerebral fungus infection and 1 a generalized meningitis

Similar to war wounds the prophylactic use of the sulfonamides in the *treatment of the burned patient* is receiving extensive application in the present war As pointed out in previous sections the lesion must be considered potentially infected but the proper handling of the burn case consists in much more than the local application of something to the wound It must consider the management of shock and certain shock like symptoms the nutrition and fluid balance and

sulfadiazine and under local use of sulfonamides Certain advances continue to be made in these broad fields some of which will bear brief repetition

Hailed at first with considerable enthusiasm, the local implantation of a sulfonamide usually sulfanilamide into a clean operative wound or a potentially infected wound has left considerable to be desired[115 468 596] It has been learned that local infection may not be completely eradicated, wound healing may be retarded and toxic effects hematuria, jaundice, may ensue When applied locally the sulfonamides will tend to keep the infection localized, however preventing tissue invasion Since the prevention of systemic invasion of bacteria after operation is a goal to be desired, the oral or parenteral administration of one of these compounds has been found to be more effective toward that end In fact combined local and systemic administration has come to be preferred sulfanilamide on or in the wound and sulfadiazine orally But meticulous surgical technique still is the prime essential The present status of the use of the sulfonamides in surgery has been summarized by Altemeier[597] 'The failure of the sulfonamides to prevent the development of wound infection reemphasizes the surgical truths that the physiologic state of the wound is of the greatest importance in determining the development of infection and that antiseptic or bacteriostatic agents have only transient anti bacterial effects and may have definite harmful effects on the wounded tissues It follows that chemotherapy in any form cannot and will not replace the surgical principles of debridement and asepsis

In *abdominal surgery* sulfaguanidine and sulfasuccidine orally will reduce the bacterial flora of the bowel[10 4 5 515 516 522] As has been discussed under sulfaguanidine Marshall[137] who introduced this compound into clinical medicine, has expressed later the idea that the use of a sulfonamide locally in the abdominal cavity and systemically at the time of operation may prove more valuable than an attempt to reduce the bacterial flora of the colon before operation That idea seems to have been borne out subsequently

Postoperative urinary tract infections are very satisfactorily prevented particularly in older individuals by the use of small doses of sulfanilamide[96] or sulfathiazole[548] 0 5 gm (gr 7½) to 1 0 gm (gr 15) a day particularly when catheterization is necessary

The prophylactic use of the sulfonamides in the treatment of *war wounds* still remains somewhat unsettled They are being used extensively however tempered by warnings of the danger of over reliance upon them[583] Their overall evaluation as prophylactic agents in the management of U S Army casualties is difficult Under the present system of management complete excision of the frequently extensive wounds is impossible It is too time consuming and may be too mutilating Wound trimming is carried out hemorrhage arrested the wound is exteriorized by generous incision and packed open Local and systemic sulfanilamide usually are applied By and large the results are good,

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Similar to war wounds the prophylactic use of the sulfonamides in the *treatment of the burned patient* is receiving extensive application in the present war As pointed out in previous sections the lesion must be considered potentially infected but the proper handling of the burn case consists in much more than the local application of something to the wound It must consider the management of shock and certain shock like symptoms the nutrition and fluid balance and

good nursing care as well as general measures to combat infection. The local application of sulfanilamide powder to the burned area has been used quite extensively in the field. It is being gradually replaced, however, by systemic sulfadiazine and more recently by penicillin to maintain an adequate blood level of drug in order to prevent invasiveness, the general spread of bacteria, septicemia and death from infection. Under careful experimental conditions the systemic administration of sulfadiazine in such cases has not seemed to be as beneficial as would be desired. Of 141 patients with burns treated systemically, 31.2 per cent became seriously infected and 19.9 per cent were trivially infected, a total incidence of 51.1 per cent. Of the patients not treated with the drug 10.4 per cent were seriously infected and 24.9 per cent trivially infected, a total incidence of only 35.3 per cent[505]. From this study, carried out by members of the National Research Council, it was concluded that although the sulfonamides minimize the general spread of infections in burns as in other wounds, they did not lessen the incidence of local infection.

For the treatment of burns, to combat the ever present danger of infection, it can be said that the value of the sulfonamides seems assured, but the procedure by which they are best used has not yet been established. Powders have caused mechanical difficulty (caking), sulfadiazine spray (Pickrell) takes 4 days to apply, the burn may remain painful and transportation may be difficult. Added to this, the size of the raw area in certain instances can permit significant absorption of the drug into the blood stream causing toxic reactions. Some investigators have advocated the routine use of one of the sulfonamides by mouth in all burn cases of appreciable extent. While there might seem to be some advantages accruing from this procedure, it has been criticized on the basis that nausea and vomiting are frequent and would add further to the hemoconcentration. Further, these drugs may aggravate or precipitate real or incipient liver damage in patients with burns. If systemic administration is desired, however, sulfadiazine or sulfathiazole have been the drugs of choice.[506]

PART IX–A

SUMMARY

The sulfonamide compounds are chemical substances that have been devel oped in the past decade for use in the treatment of certain bacterial infections They originate from diazo compounds that have been known and used as a base in the dye industry of Europe for many years. One of these the original sub stance that was introduced into clinical medicine by Dr Gerhardt Domagk in 1935 was known as prontosil a complex chemical in which on analysis the mole cule para aminobenzenesulfonamide was found to be the active principle To para aminobenzenesulfonamide was given the name sulfanilamide a substance which is synthesized easily and from which many derivative have been devel oped Literally thousands of derivatives have been produced but only a few of them have been found to be tolerated sufficiently well by the human being to be utilized in the treatment of bacterial infections The developments which followed have established a new era in the treatment of the diseases of mankind

As *chemicals* the sulfonamides are benzene ring compounds with an amino grouping in the para position The compounds developed by substitutions in the para amino group for the most part have not been very satisfactory as chemo therapeutic agents The main advances in new derivatives and compounds have taken place in substitutions and additions to the sulfonamide group at the oppo site end of the benzene ring The substitutions have included chiefly pyridines thiazoles pyrimidines guanidines and succinic acid The resulting compounds have been introduced as sulfapyridine sulfathiazole sulfadiazine sulfaguanidine and succinylsulfathiazole (sulfasuccidine) all of which have been accepted for clinical use by the Council of Pharmacy and Chemistry of the American Medical Association A methyl radicle has been added to some of the above as in sulfa merazine and sulfamethazine but they have neither received widespread use nor been accepted by the Council so far

Most of these compounds are slightly acid substances but may act as ampho lytes They are synthesized very readily appearing as crystals with varying solubilities Sulfanilamide is the most soluble sulfadiazine the least Their absorption in the body distribution in the tissues therapeutic activity excretion and toxic effects depend in part on the solubility To increase their solubility sodium salts of all the compounds except sulfanilamide and sulfaguanidine have been formed to permit more rapid administration and higher dosage The sodium salts are used chiefly intravenously and may be used intramuscularly and subcu taneously

Their *mode of action* is chiefly by producing bacteriostasis and under certain circumstances some bacteriolysis They inhibit the growth of bacteria thereby limiting bacterial powers of invasiveness which permits the defense mechanisms of the body to overcome the infection Various theories have been proposed as to the mechanism of this action the best supported being that the activity is due to the blocking of an enzyme system It is considered that bacteriostasis depends upon the specific inhibition of an enzymatic reaction involving para aminobenzoic acid or similar substances The enzymes are protein in nature, and inhibition of their action involves some form of chemical interaction between the inhibitor and the enzyme In further elucidation of this mechanism it has been found that the ionic portion of the sulfonamide molecule considered in terms of an acid dissociation constant of the drug (pK) is the active component involved in the bacteriostasis

In their *pharmacology* the sulfonamides except for sulfaguanidine and sulfa succidine when taken orally are absorbed rather rapidly from the intestinal tract are retained in the blood stream to be distributed throughout the body for a period of time and are excreted chiefly by the kidneys Their distribution in the body and equilibria in body fluids and tissues are related to the albumin binding properties of the drug and their ionic activity Both the protein binding and ionic activity are influenced by the hydrogen ion concentration of the medium being increased within certain limits by alkalinity

The pharmacological properties that are desirable with these drugs are rapid absorption to attain an effective blood level against the invading organism, maintenance of an effective blood level to continue to act on the bacteria and adequate excretion Most important of course is that the drug will eliminate the activity of the offending bacteria and at the same time be least harmful preferably innocuous to the human body Unfortunately such a state of perfection has not been reached, but it may be said that the toxicity of these compounds to the human subject is slight in comparison with their beneficial effects Being chemical poisons to the body they are partly detoxified by conjugation in the liver with the formation of an acetyl salt The acetyl salt of these compounds is without therapeutic effect and is excreted in the urine With the use of these compounds in therapy it has been found that adequate fluids must be administered Fluids promote distribution of the chemical in the body as well as aid in its *elimination* in the urine If fluids are forced to excess however, the effective concentration of the drug may be diluted thereby with resulting ineffectual blood levels In addition adequate fluid intake always has been considered to be good treatment in any bacterial infection

The sulfonamide compounds differ from all other antiseptics in that they are the first chemotherapeutic agents that can be administered by mouth and at the

same time can be effective against a wide variety of organisms They are most effective systemically against virulent organisms organisms that are invading and spreading rapidly through body tissues and organisms in deep rather than superficial infections They are often ineffective when undrained purulent exudates exist due to the antisulfonamide effect of protein degradation products especially para aminobenzoic acid For the best results in such circumstances the abscess should be drained well and then chemotherapy instituted These drugs may be ineffective also against overwhelming infections in which toxicity is very great The best results are obtained by their use early in any infection in which they are indicated

For most infections these drugs are to be *administered* by mouth in doses sufficient to attain and maintain an adequate blood level against the organism involved In general it is a good rule to strike quickly with rather large initial doses of 3 0 to 6 0 gm to build a blood level rapidly to maintain a blood level of 5 to 10 mgm per 100 c c until the temperature has returned to normal for 3 to 4 days and the patient is well on the road to recovery then to stop the drug quickly and completely With patients who are severely ill or who cannot take the drug by mouth usually it is advisable to begin therapy with a 5 0 per cent solution of the sodium salt in distilled water intravenously or a 0 5 to 2 0 per cent solution subcutaneously for rapid attainment of an effective blood level which may need to be 10 0 to 20 0 mgm per 100 c c The sodium salts of some of the compounds may be used in 25 to 33 per cent strength intramuscularly when desired With the exception of sulfanilamide the rectal administration of any of the other compounds for systemic effect is without benefit The intrathecal administration of them seldom is necessary For individuals who are ambulatory, smaller doses than the above often are adequate and much safer from a standpoint of toxic possibilities

In powdered form or incorporated into ointments these drugs may be used locally in the treatment of tissue wounds burns compound fractures eye and ear conditions and in operations upon the peritoneal pleural or cranial cavities Their local bacteriostatic effect depends upon their solubility and the concentration reached in the tissues For such application sulfanilamide is preferred Its dangers lie in the fact that too much powder or ointment should not be applied for it can irritate tissues its erratic sometimes appreciable absorption into the blood stream can lead to toxic blood levels The present tendency where local application is indicated is to apply sulfanilamide and in addition to use sulfadiazine by mouth or parenterally for its systemic effect Sulfadiazine is preferred over sulfanilamide because with it a high blood level is more easily maintained Here caution is necessary however for a summation of blood levels from both local and systemic administration may occur with resulting toxic reactions The

sodium salts should not be applied to mucosal or serosal surfaces because of their marked alkalinity.

The introduction of numerous sulfonamide compounds into clinical medicine has been the outgrowth of the desire to find the most potent chemical substance against the greatest variety of organisms which at the same time will be the least toxic to the host. The result has been a variety of successful chemotherapeutic agents with the hope that each one, as it became successively available would replace those that had gone before it. After further study and trial however it has been found that each one is selectively effective against certain organisms with some better than with others. The result is that each one has its place but not to the exclusion of the others. For the comparative effect of the various compounds against the various organisms and diseases the reader is referred to the sections on the respective drugs and the included tables. The following discussion will be limited to a few broad generalizations concerning some of the more common bacterial infections.

Against most *streptococcal* infections the sulfonamide compounds are effective better against the hemolytic than the non hemolytic varieties. Though all may be effective sulfadiazine at present is the drug of choice because a satisfactory blood level with it can be sustained better than with sulfanilamide and it is grossly less toxic than sulfapyridine or sulfathiazole.

For *staphylococcal* infections sulfathiazole and sulfadiazine are of about equal value the former perhaps slightly better than the latter yet both leave much to be desired. The present indications suggest that another substance penicillin, in all probability will replace the sulfonamide compounds in the treatment of staphylococcal infections particularly in the acute stage. When sulfathiazole or sulfadiazine are used they should be given in large doses, preferably both intravenously and orally, along with proper drainage of any existing abscesses when possible. For urinary tract infections due to this organism small doses usually are sufficient for good results.

In the treatment of *pneumococcal* infections all three drugs, sulfapyridine, sulfathiazole and sulfadiazine are remarkably effective. Sulfamerazine gives promise of being equally beneficial but it has not yet received extensive trial. At the present time sulfadiazine is the drug of choice because of less toxicity than sulfapyridine or sulfathiazole. Sulfadiazine in an initial dose of 2.0 to 4.0 gm followed by 1.0 gm every 4 hours is effective against nearly all types of the pneumococcus. The drug rapidly clears the blood stream of pneumococci unless such complications as endocarditis or meningitis are present. There is no optimum blood level but as a guide a level of 5 to 10 mgm per 100 c c has been found to give over 90 per cent recovery in the average series of cases. In the ordinary case of pneumococcus pneumonia adjuvant serum therapy has not been of benefit

neither has it seemed to reduce the mortality in patients severely ill with bacteremia Horse or rabbit serum is to be used when the organism is refractory to sulfonamide drug or when the patient cannot tolerate the chemicals The sulfonamides generally are ineffective against pneumococcal meningitis

Sulfadiazine is at present the drug of choice in the treatment of *meningococcic infections* although sulfapyridine and sulfamerazine are effective also With a rapid and sustained high blood level obtained by the administration of the sodium salt intravenously followed by oral medication the blood stream usually is cleared of organisms promptly and in the case of meningitis this results in over 90 per cent recovery Here again the adjuvant use of serum is of doubtful benefit but has its place when the sulfonamide is ineffective or the patient cannot tolerate the drug Originally with these drugs it was advised that they be given intrathecally but subsequently it has been learned that such procedures are not necessary They penetrate adequately the meninges from the blood stream to give levels in the spinal fluid from 50 to 80 per cent of that present in the blood

In the treatment of *gonorrhea* the sulfonamide compounds have come to be used to a large extent in the treatment of the patient while ambulatory Sulfathiazole has shown slightly better results than the others but sulfapyridine and sulfadiazine are effective also Sulfamerazine is of some benefit but sulfanilamide is of practically no use in this disease On oral doses of 3 0 to 5 0 gm daily the discharge stops and the urine becomes clear in 5 to 7 days Urethral irrigations with these drugs are of no benefit In chronic cases with posterior urethritis in the male larger doses preferably with hospitalization may be necessary In not a few instances gonococci have been found to be or to become sulfonamide resistant and for these the new substance penicillin seems to be very effective

For *infections of the urinary tract* sulfathiazole and sulfadiazine are both effective against numerous pathogenic organisms None of them is of any use against *Streptococcus fecalis* In the treatment of such infections small doses by mouth often are effective for it has been realized that beneficial effects are not dependent entirely on a high concentration of the drug in the urine In this consideration it is most important to be cognizant of the pathological changes associated with the urinary tract disturbances for in the presence of tumors obstruction calculi abscesses and so on the drugs may be useless Surgical corrective measures should be instituted along with these drugs to obtain the best results

For the treatment of *infections of the gastrointestinal tract* two drugs have been produced sulfaguanidine and sulfasuccidine A third sulfathalidine holds promise but has not yet received adequate clinical trial The desirable features of both these drugs for intestinal antisepsis are that they are little absorbed thereby giving a high concentration of the chemical in the gut Sulfaguanidine remains intact for the most part but sulfasuccidine is broken down in the intes

tine to succinic acid and sulfathiazole, the latter being poorly absorbed in the colon Both act by reducing appreciably the coliform organisms in the intestines and act rather specifically against the bacilli of dysentery Neither is significantly effective against amebae or the active stage of typhoid fever When used, they are to be administered by mouth Large doses may be required, 10 0 to 20 0 gm a day These drugs have been tried also as preoperative antiseptics in gastrointestinal surgery to avoid postoperative complicating infections They have met with some degree of success

In numerous diseases and under certain circumstances these drugs may be totally *ineffective* With a few possible exceptions they are relatively innocuous against the virus spirochetal mycotic and protozoan infections and certain specific disease such as naturally acquired malaria and tuberculosis They may be helpful in eliminating the carrier state but are generally ineffective against typhoid and paratyphoid fevers With certain organisms against which the drug are usually active there may occur strains that are resistant to the action of the drug Such *drug resistance* also may be acquired by bacteria both in vitro and in vivo and is brought about chiefly by the use of small, ineffective doses of the drug given over a considerable period of time Occasionally under such circumstances a change to one of the other drugs will cause bacteriostasis and effect a cure but more frequently the other compounds are ineffective also against such strains

The *toxic effects* of these compounds manifest themselves in a wide variety of forms Comparatively speaking however as drugs they are very mildly toxic when compared to the benefits derived from them In a general way between 10 and 15 per cent of individuals given the drugs manifest toxic reactions most of which are mild These effects may be the result of idiosyncrasy or allergy on the part of the patient or the result of cumulative effect over a period of time Sensitization may be developed i e with no untoward results occurring with the first use of the drug but toxic symptoms becoming manifest upon subsequent administration of the chemical Some of the reactions seem analogous to serum disease and may be due to a sensitization to the chemical or to one of the radicles of which it is composed

The toxic effects may manifest themselves in nearly any system or tissue in the body Fortunately most of them are mild and transient in character when recognized and treated properly but severe illness and death can result Cyanosis is rather peculiar to sulfanilamide Nausea and vomiting also considered mild symptoms, are seen chiefly with sulfanilamide, sulfapyridine and sulfathiazole less commonly with the others The same three drugs also seem to cause deleterious effects on the formed elements of the blood more than do the newer compounds A mild depression of hemoglobin and the red blood cell count from pro-

longed use need cause no concern but acute hemolytic anemia agranulocytosis and hemorrhagic purpura are serious manifestations to be watched for Any of these compounds may cause a skin rash which may take on any one of many forms none of which is specific for these drugs Sulfathiazole has been the only one to cause a significant number of erythema nodosum like lesions Likewise any of them may cause a febrile reaction which is considered to be a sensitization phenomenon Any one of them can give rise to central nervous system effects but the methylated derivatives seem more prone to produce them Dizziness giddiness and headache usually are transient phenomena but neuritis and peripheral nerve palsies may persist

Sulfapyridine sulfathiazole sulfadiazine and sulfamerazine have as their most common reaction an effect on the kidneys with the precipitation of acetyl crystals in the urine the production of hematuria renal calculi diminished renal function and anuria Sulfanilamide has not been known to cause any toxic effects on the kidneys The deaths from these drugs have been relatively few considering their widespread use When death could be attributed to them it has been due as a rule, to either kidney involvement agranulocytosis or to liver damage

With the use of these drugs in the treatment of infections constant careful observation of the patient must be made in order to detect early any toxic effects that may be attributed to the medication For such manifestations as cyanosis nausea vomiting headache giddiness and so on the drug need not be stopped For any of the other symptoms however the drug had better be stopped or at least proceeded with very cautiously as they may be the heralding signs of more serious reactions With such exhibitions of toxicity as acute hemolytic anemia agranulocytosis gross hematuria anuria jaundice skin rashes or drug fever the chemical must be stopped immediately and fluids forced Throughout treatment with these drugs it is advisable to insure a daily output of 1 200 to 1 500 c c of urine The only preventive measures that have been advanced with the use of the sulfonamide compounds are the adjuvant administration of urea or alkali Both of these have been introduced for the purpose of minimizing the toxic effects on the kidneys The use of alkalies particularly in the form of sodium bicarbonate has received the most study and application In practice for both prophylaxis and therapy of the renal complications the alkali should be administered in doses sufficiently large to keep the pH of the urine at or above 7 0 This may require from 15 0 to 20 0 gm per day The use of adjuvant alkali increases absorption of the drug may enhance the bacteriostatic activity and promotes the excretion of the chemical in the urine

The use of the sulfonamide compounds has created a new era in medical therapeutics which has been truly phenomenal These chemicals are effective by

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PART X

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mouth as well as parenterally in overcoming infections due to a wide variety of organisms They are synthesized easily, which allows for mass production and relatively low cost in the treatment of disease Although they leave considerable to be desired, particularly on account of their inefficacy against a still impressive list of diseases and infections and of their more undesirable toxic effects, their use has been so successful and so universal that they seem destined to remain as very frequently used chemotherapeutic agents for some time to come

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CHAPTER XXX B

PENICILLIN IN THE TREATMENT OF INFECTIONS

By CHESTER S. KEEFER AND DONALD G. ANDERSON

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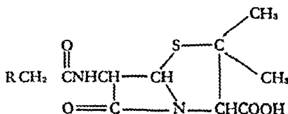
in so many different diseases. It was in 1942 that the first patient was treated adequately with penicillin in the United States.

While it is impossible to assess completely all of the benefits that have flowed from the use of penicillin, it can be said that it is a substance of great antibacterial power and it is nontoxic in maximum therapeutic doses in man. It is highly effective against a wide variety of microorganisms of the gram positive group as well as against several organisms of the gram negative group. It is also potent against an entirely different group of infectious agents such as *Treponema pallidum*.

It has been responsible for the reduction of the fatality rate in more diseases than any other chemotherapeutic agent; it shortens the course of many infectious disorders; it saves many days of illness and disability. No other agent can do so much.

Chemistry

At least four different penicillins have been crystallized from the products of the growth of *Penicillin notatum* and *Penicillin chrysogenum*. They have been designated as Penicillin F, G, X, K. In England these penicillins are known as Penicillin I, II, III and K respectively. The empirical formula for the basic structure has been stated to be $C_9H_{11}O_4SN$. Attached to this structure are variable aliphatic or aromatic radicals designated as R in the formula.



History

Penicillin was first described by Fleming in 19 8 but it remained for Florey and his associates to call attention to the great potential value of this agent in the treatment of systemic bacterial infections Following large scale production in the United States and extensive clinical testing in a wide variety of infections penicillin was acclaimed as one of the most potent and powerful antibacterial agents ever discovered Certainly no other therapeutic agent has caused more discussion No other anti infective agent has been used so widely with such successful results

Small amounts of penicillin have been synthesized by duVigneaud Carpenter Holley, Livermore and Rachele, but insufficient quantities have been available for clinical testing

Penicillin Standards

All batches of penicillin are certified by the Food and Drug Administration before they are released by the manufacturers for sale These certified products are studied by the manufacturers in an elaborate manner before they are tested by the Food and Drug Administration The rules and regulations for certification have been published in the Federal Register in April, 1947 and they are amended from time to time in order to meet new conditions All information concerning the stability of the product and other essential features are contained on the label and package inserts These should be read carefully by the physician who uses the product

Stability

With the improvement in the art of manufacturing penicillin the stability of the various preparations both in powder form and in solution has increased Recent studies by Regna indicate that there may be no loss of potency during a period of at least 350 days, when the dry powder is stored at 0 to 5 C Even at 37 C the dried powder retains its full potency for at least 60 days Kirby has demonstrated that solutions of penicillin may be kept at room temperature (2 C) for 1 week without evidence of deterioration and that most samples retain full activity for 10 to 12 days When the temperature is raised to 37 C the full potency persists for only 4 days It is plain therefore that penicillin is more stable in powder form than in solution and more stable in cold than at room or body temperature

Dosage Forms for Use in Treatment of Systemic Infections

Amorphous Penicillin—Amorphous penicillin is now used less and less because it is a mixture of penicillins that is to say it contained penicillin G K F Penicillin G is the product about which we have the

Table I

The Several Penicillins Produced By

P notatum and *P chrysogenum**

American nomenclature PENICILLIN	British nomenclature PENICILLIN	In which R (in the penicillin formula) equals
F	I	Δ-pentenyl $CH_2CH=CHCH_2CH_3$
G	II	benzyl CH_2-⬡
X	III	p hydroxybenzyl CH_2-⬡-OH
K	K	n heptyl $CH_2CH_2CH_2CH_2CH_2CH_2CH_3$

* The relative proportions of these species present in any commercial preparation of the drug vary with the manner of propagation of the mold e g by surface or deep cultures with various methods of enrichment of the medium used for growth with various recovery procedures Apparently also they vary inexplicably from time to time even when conditions of growth remain the same

CHARACTERISTICS

The only crystalline penicillin available for clinical use is penicillin G or benzyl penicillin Crystalline penicillin G was obtained first by MacPhillamy and Wintersteiner of the Squibb Institute for Medical Research in July 1943 Crystalline penicillin F and G assays at 1 667 units per milligram crystalline X 900 U/mgm and crystalline K 2,300 U/mgm

There are several salts of benzyl penicillin that have been used the sodium the potassium procaine and aluminum salts The sodium and potassium salts are extremely soluble in water physiological saline or dextrose solution The procaine salt is only slightly soluble but it can be suspended in oil or aqueous solution for intramuscular injection

units may be used daily for aerosol treatment The solutions are passed through a DeVilbiss No 40 or a vaponephrin nebulizer using a hand bulb or a constant pressure of oxygen flowing at the rate of 6 liters a minute

Penicillin in Ointments—Ointments for the local or topical application of penicillin are available for use in the conjunctivae or on the skin They are stable and useful for the treatment of infections locally They should be used sparingly and for a brief period of time since sensitization may arise following the use of penicillin in this way much more often than when it is taken orally or given parenterally

Inhalation of Penicillin Powder—Preparations of finely powdered penicillin G are available for inhalation into the upper or lower respiratory passages The purpose of these inhalations is to place the crystals in contact with the mucous membranes of the respiratory passages and have them dissolved slowly by the secretions of the nose throat and bronchi Too few cases have been studied to make any statements concerning the value of this type of treatment

Penicillin Procaine G for Aqueous Injection—By the addition of a harmless detergent penicillin procaine G has been prepared for aqueous injection This preparation has the advantage that it can be injected as an aqueous suspension and there is a delay in the absorption of the penicillin from the muscles in much the same way as the suspension of procaine penicillin in oil Sterile aqueous suspensions may be kept at room temperature for a period of one week without any significant loss of potency This preparation has the advantage that it contains neither oil nor wax It can be injected with great ease The syringes and needles do not have to be dry There is no difficulty in the cleaning of syringes and needles following its use and the blocking of the needle during injection is minimized More important however is the fact that in our hands it is therapeutically effective and the plasma concentrations of penicillin are maintained at detectable levels for 4 hours or longer following a single injection of 300 000 units

Dosage

An adequate dose of penicillin might be defined as that amount that will cure the patient with a susceptible infection in the shortest period of time and eliminate the infecting organisms from the body Since there are so many variables in the treatment of any specific

greatest amount of information and which we know is highly effective In spite of the fact that many samples of amorphous penicillin contained at least 85 per cent penicillin G it became unpopular as an agent for the treatment of all infections because it was shown that penicillin K was relatively ineffective in the treatment of experimental syphilis and less effective than penicillin G in the treatment of experimental streptococcic and pneumococcic infection in mice At present there are some preparations of amorphous calcium penicillin in peanut oil and wax or amorphous aluminum penicillin in oil available for use, but very little amorphous penicillin is now available for use in aqueous preparations

Crystalline Penicillin G—This is the most widely used preparation for parenteral and oral use The crystals are dispensed for aqueous solutions or suspended in peanut oil and wax for parenteral use They are combined with buffers in tablets for oral use and combined with ointments for topical use

Salts of Penicillin—There are two commonly used salts of penicillin, the sodium and the potassium They are both highly soluble and active There is no choice between the two salts insofar as therapeutic results are concerned Recently the procaine salt of benzyl penicillin (penicillin G) has been prepared and it is being used very widely This salt is soluble in 0 7 per cent aqueous solution and contains approximately 50 per cent procaine It is suspended in sesame oil or in aqueous solution to which a detergent has been added, and it is used for intramuscular injection It is absorbed slowly so that, following a single injection of 300 000 units penicillin is found in the blood for as long as 24 to 48 hours in many patients Also aluminum monostearate has been combined with oil and mixed with procaine penicillin G to delay its absorption

Oral Penicillin—The ideal way to give any drug is by mouth It is now established that penicillin can be absorbed from the gastrointestinal tract but it requires about five times as much penicillin when it is given by mouth, to obtain comparable plasma concentrations, as it does when penicillin is given by the intramuscular route That penicillin is effective by the oral route has been demonstrated repeatedly by many observers One of the drawbacks to its more widespread use has been its cost

Aerosol Penicillin—Crystalline penicillin G dissolved in physiological salt solution, is used as an aerosol for the treatment of bronchopulmonary disease or chronic paranasal sinusitis From ₋00,000 to 1,000 000

When glutamic acid enters the microorganisms it is available in the free state and serves as a source of amino acid for protein synthesis and other metabolic functions of growing cells When gram positive organisms are exposed to penicillin glutamic acid is not assimilated The level of glutamic acid within the cell decreases and growth is not sustained There is correlation between the amount of penicillin needed to prevent the growth of organisms and the amount needed to prevent assimilation of glutamic acid by the bacteria Moreover there is a quantitative relation between the assimilation affinity of the organism for glutamic acid and penicillin sensitivity of the organism

Finally, one very important observation has been made that gives support to the view that the action of penicillin involves a disturbance in the uptake of susceptible bacterial cells Strains of staphylococcus aureus that become highly resistant to penicillin not only lose their ability to assimilate glutamic acid but they become gram negative in their staining reactions and like other gram negative organisms then they are able to synthesize all of its amino acid requirements from ammonia and glucose in the presence of thiamine

These observations assist then in their understanding of the mode of action of penicillin

Speaking broadly penicillin is both bacteriostatic and bactericidal The destructive power of penicillin in vitro and probably in vivo is greatest during the period when the bacteria are multiplying most rapidly It has been demonstrated in vitro that the greatest number of organisms are killed during the first 5 to 8 hours after exposure to penicillin The organisms that survive this initial period may not be killed for 4 to 36 hours in spite of the fact that they are exposed to the continuing action of penicillin When the organisms that survive the 5 to 8 hours period are removed from the environment of penicillin and re inoculated into fresh broth without penicillin it is found that their lag period is slightly prolonged but once they start to reproduce they are highly susceptible once more to the action of penicillin From such in vitro observations it has been suggested that penicillin must be maintained at a minimal effective concentration for a sufficiently long period of time so that all organisms are destroyed and their reproduction prevented

It has been suggested further that recovery from a given infection in man will occur once the minimum concentration of penicillin is maintained in the blood and tissues for a sufficient period of time to kill

infection in man it is extremely difficult to make any categorical rules concerning dosage in a given infection It is important nevertheless to develop the best methods of treatment with penicillin so that optimum results may be obtained with the least discomfort and expense to the patient One of the greatest difficulties that faces us in attempting to assess dosage of penicillin is the fact that it is a non toxic drug, that is to say very large amounts of penicillin can be given for long periods of time without producing any signs of intoxication When any drug is non toxic, it is difficult to determine the minimum effective dose because the temptation is great to give larger amounts of the drug than are necessary for producing a favorable clinical result

Other factors of importance in dosage are the type of infection and its location Everyone knows that penicillin is an agent that inhibits the growth of a wide variety of bacteria but different species of bacteria vary enormously in their resistance to the action of the drug In fact, different strains of organisms within a species often will vary in their susceptibility to penicillin All of these factors make it difficult to define the minimum effective dose for each infection In spite of the difficulties involved it is well to review some of the information concerned with (1) the mode of action of penicillin (2) the effective plasma concentrations that inhibit the growth of organisms and (3) the time dose relationships

Antibacterial Action

The exact mechanism of the antibacterial action of penicillin is not yet understood It has been presumed that penicillin like the sulfonamides acts by interfering with some essential process in the metabolism of susceptible bacteria Like many other antibacterial agents penicillin may be either bactericidal or bacteriostatic It has no action on bacteria that are in the resting phase It does not interfere with the uptake of oxygen The recent investigations of Gale and his associates strongly suggest that penicillin may exert its action upon bacteria by disturbing the uptake of amino acids by susceptible cells It has been demonstrated that gram-positive organisms are capable of assimilating and concentrating lysine and glutamic acid from the medium Lysine enters the cells by diffusion but glutamic acid cannot pass the cell wall unless energy is supplied by some exergonic metabolism such as the fermentation of glucose

must be to be susceptible to penicillin therapy. In general it can be said on a basis of clinical experience that infections caused by organisms that are inhibited in vitro by a concentration of 0.1 unit or less per cubic centimeter are uniformly susceptible to penicillin therapy. It would further appear that infections caused by organisms that require concentrations of 1.0 unit or more for complete inhibition may not respond at all or very slowly to penicillin therapy unless massive doses are given. Against organisms whose sensitivity is intermediate between these two groups penicillin has been observed to be clinically effective on occasions.

The bacterial species that are generally considered at present to be susceptible to penicillin, as indicated by laboratory and clinical studies, are listed in Table I. As a rule penicillin has proved to be effective in the treatment of infections caused by these organisms although in individual cases the site or extent of the infection, the general condition of the patient or the presence of complications may preclude successful therapy.

TABLE I

Staphylococcus albus	*Clostridium novyi*
Staphylococcus aureus	*Clostridium oedematis maligni*
Streptococcus pyogenes	*Clostridium perfringens*
Nonhemolytic streptococci	*Clostridium tetani*
Anaerobic streptococci	*Corynebacterium diphtheriae*
Diplococcus pneumoniae	*Treponema pallidum*
Neisseria gonorrhoeae	*Treponema pertenue*
Neisseria intracellularis	*Streptobacillus moniliformis*
Bacillus anthracis	*Spirillum minus*
Clostridium botulinum	*Borrelia novyi*
Clostridium histolyticum	*Actinomyces bovis*

It is well recognized that even with these susceptible species differences are found in the sensitivity to penicillin of various strains. In most instances these differences are not sufficiently great to be clinically significant but occasional strains are encountered that possess a naturally high resistance to penicillin. The susceptible species in which naturally resistant strains have been reported are the staphylococcus, nonhemolytic streptococcus, anaerobic streptococcus and actinomyces.

off large numbers of organisms and to prevent their reproduction When the minimum effective concentration necessary to produce a remission is not maintained for a much longer period of time than that necessary to reduce the total number of organisms, then relapse will occur Both the concentration of penicillin and the time of exposure of the organisms are important It would appear that the total time organisms are exposed to minimum effective concentrations of penicillin is more important than the exposure of organisms to high concentration of penicillin for a short period of time alternating with penicillin-free periods There are good reasons for believing that the minimum effective level in man need not be continuous throughout the 24 hour period in order to obtain recovery from infection but the minimum effective concentration must be maintained for a sufficiently long period of time so that the organisms will be destroyed or prevented from entering a phase of active growth once again

It has been demonstrated many times that the in vitro action of penicillin against susceptible organisms may be either bactericidal or bacteriostatic In the concentrations that are achieved in vivo its effect is chiefly bacteriostatic In the treatment of infections the drug inhibits the growth of bacteria but the actual elimination of the infecting organisms probably is accomplished by the cellular and humoral defense mechanisms of the host Evidence to support this view is derived from the fact that with the exception of uncomplicated gonorrhea and meningococcemia penicillin therapy must be continued in most infections for a minimum of 5 to 7 days to effect complete recovery In many diseases much more prolonged therapy is necessary before the infecting organisms are entirely eliminated

Unlike the sulfonamides penicillin is not inhibited by pus, peptones or the breakdown products of tissue autolysis It has been reported recently, however, that human serum is capable of inactivating penicillin It has been assumed that this phenomenon is due to the absorption of penicillin inactivators that have been formed in the intestinal tract

While the antibacterial action of penicillin is selective, susceptibility to it is to a certain extent a relative rather than an absolute characteristic Certain pathogenic organisms are inhibited by minute concentrations of the drug whereas others are not influenced adversely by very high concentrations Between these two extremes is a third group of organisms that is inhibited in vitro by intermediate concentrations of the drug

It has not yet been determined how sensitive to penicillin an organism

must be to be susceptible to penicillin therapy In general it can be said on a basis of clinical experience that infections caused by organisms that are inhibited in vitro by a concentration of 0 1 unit or less per cubic centimeter are uniformly susceptible to penicillin therapy It would further appear that infections caused by organisms that require concentrations of 1 0 unit or more for complete inhibition may not respond at all or very slowly to penicillin therapy unless massive doses are given Against organisms whose sensitivity is intermediate between these two groups penicillin has been observed to be clinically effective on occasions

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Neisseria intracellularis	*Streptobacillus moniliformis*
Bacillus anthracis	*Spirillum minus*
Clostridium botulinum	*Borrelia novyi*
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It is well recognized that even with these susceptible species differences are found in the sensitivity to penicillin of various strains In most instances these differences are not sufficiently great to be clinically significant but occasional strains are encountered that possess a naturally high resistance to penicillin The susceptible species in which naturally resistant strains have been reported are the staphylococcus nonhemolytic streptococcus anaerobic streptococcus and actinomyces

In Table II are listed the important pathogenic bacteria that are generally considered to be insusceptible to the concentrations of penicillin that can be achieved in the blood and tissues

TABLE II

Escherichia coli	*Haemophilus pertussis*
Eberthella typhosa	*Streptococcus fecalis*
Shigella dysenteriae	*Brucella melitensis*
Salmonella enteritidis	*Vibrio cholerae*
Salmonella paratyphi	*Pasteurella pestis*
Proteus vulgaris	*Pasteurella tularensis*
Pseudomonas aeruginosa	*Mycobacterium tuberculosis*
Klebsiella pneumoniae	*Plasmodium vivax*
Haemophilus ducreyi	Yeasts
Haemophilus influenzae	Molds

The action of penicillin on viruses and rickettsia is not entirely clear Experimental infections in mice with murine typhus and the viruses of psittacosis and ornithosis have been reported to be influenced favorably by the administration of very large doses of penicillin On the other hand the use of penicillin in virus and rickettsial infections in man has been totally ineffective When such infections are complicated by secondary infections caused by bacteria that are sensitive to the drug, penicillin therapy may be of value in controlling the secondary infection

Some confusion exists also as to the effectiveness of penicillin therapy in experimental Weil's disease Working with guinea pigs Heilman and Herrell have reported that the administration of penicillin greatly reduced the mortality rate Augustine, Weinman and McAllister also working with guinea pigs reported that the drug had no curative value after the appearance of clinical manifestations of the disease

The objective in the treatment of any patient then is to maintain penicillin at a minimum effective concentration for a sufficiently long period of time so that the infecting organisms will be destroyed or prevented from entering a phase of active growth again This statement naturally raises two questions (a) What is a minimum effective level and (b) What is the time interval between injections in man that is required in order to obtain the optimum results?

Minimum Effective Plasma and Tissue Concentrations of Penicillin

Let us turn our attention briefly to the question of the minimum effective level of penicillin in the blood and tissues. Theoretically the minimum effective level of penicillin in the blood and tissues would be that amount that would cause complete inhibition of the growth of organisms and their destruction. The determination of minimum effective levels of penicillin that will kill organisms in the test tube is much easier than the minimal effective plasma and tissue concentrations in the human body. Moreover it is widely recognized that one cannot in every instance transfer in vitro activity to in vivo conditions with penicillin. Nevertheless the sensitivity of a given organism to penicillin gives one a rough approximation of the effective concentrations of penicillin that will be needed to inhibit the growth of organisms at the site of the infection. The plasma concentration of penicillin can be determined readily. The concentration of penicillin in the tissues may be more difficult to ascertain. We know however that considerable differences exist between plasma and tissue concentrations.

In general it has been shown that the concentration of penicillin that can be delivered to the tissues (except spinal fluid, organized thromboses, abscesses) is between 10 and 50 per cent of that in the plasma. Therefore for any desired concentration in the tissues it would be well to maintain a concentration of penicillin 2 to 10 times that in the circulating blood. As an example one could say that if the sensitivity of an organism in vitro was 0.2 unit per ml then it would be desirable to maintain a plasma concentration of 0.4 or 2 unit per ml in order that the tissue concentration would be approximately 0.2 unit. While this is perhaps somewhat theoretical it at least gives one a rough guide to the minimum effective level of penicillin in blood and tissues.

It can be said then that the minimum effective plasma and tissue concentration should be at least 2 to 10 times that amount of penicillin that will produce a bactericidal effect against the organism in vitro.

From this discussion of dosage it can be said that the therapeutic activity of a given dose of penicillin will depend upon the amount that is given and the total length of time that penicillin remains at the maximum bactericidal level in the blood and tissues plus the time required for the organisms to recover from penicillin and begin multiplication. We know from experience that it is unnecessary to maintain the concentration of penicillin in the blood and tissues continuously at

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Haemophilus ducreyi	Yeasts
Haemophilus influenzae	Molds

The action of penicillin on viruses and rickettsia is not entirely clear Experimental infections in mice with murine typhus and the viruses of psittacosis and ornithosis have been reported to be influenced favorably by the administration of very large doses of penicillin On the other hand the use of penicillin in virus and rickettsial infections in man has been totally ineffective When such infections are complicated by secondary infections caused by bacteria that are sensitive to the drug, penicillin therapy may be of value in controlling the secondary infection

Some confusion exists also as to the effectiveness of penicillin therapy in experimental Weil s disease Working with guinea pigs Heilman and Herrell have reported that the administration of penicillin greatly reduced the mortality rate Augustine Weinman and McAllister also working with guinea pigs, reported that the drug had no curative value after the appearance of clinical manifestations of the disease

The objective in the treatment of any patient then is to maintain penicillin at a minimum effective concentration for a sufficiently long period of time so that the infecting organisms will be destroyed or prevented from entering a phase of active growth again This statement naturally raises two questions (a) What is a minimum effective level and (b) What is the time interval between injections in man that is required in order to obtain the optimum results?

Minimum Effective Plasma and Tissue Concentrations of Penicillin

Let us turn our attention briefly to the question of the minimum effective level of penicillin in the blood and tissues. Theoretically the minimum effective level of penicillin in the blood and tissues would be that amount that would cause complete inhibition of the growth of organisms and their destruction. The determination of minimum effective levels of penicillin that will kill organisms in the test tube is much easier than the minimal effective plasma and tissue concentrations in the human body. Moreover, it is widely recognized that one cannot in every instance transfer in vitro activity to in vivo conditions with penicillin. Nevertheless, the sensitivity of a given organism to penicillin gives one a rough approximation of the effective concentrations of penicillin that will be needed to inhibit the growth of organisms at the site of the infection. The plasma concentration of penicillin can be determined readily. The concentration of penicillin in the tissues may be more difficult to ascertain. We know, however, that considerable differences exist between plasma and tissue concentrations.

In general, it has been shown that the concentration of penicillin that can be delivered to the tissues (except spinal fluid, organized thromboses, abscesses) is between 10 and 50 per cent of that in the plasma. Therefore, for any desired concentration in the tissues, it would be well to maintain a concentration of penicillin 2 to 10 times that in the circulating blood. As an example, one could say that if the sensitivity of an organism in vitro was 0.02 unit per ml, then it would be desirable to maintain a plasma concentration of 0.04 or 0.2 unit per ml in order that the tissue concentration would be approximately 0.02 unit. While this is perhaps somewhat theoretical, it at least gives one a rough guide to the minimum effective level of penicillin in blood and tissues.

It can be said then that the minimum effective plasma and tissue concentration should be at least 2 to 10 times that amount of penicillin that will produce a bactericidal effect against the organism in vitro.

From this discussion of dosage it can be said that the therapeutic activity of a given dose of penicillin will depend upon the amount that is given and the total length of time that penicillin remains at the maximum bactericidal level in the blood and tissues plus the time required for the organisms to recover from penicillin and begin multiplication. We know from experience that it is unnecessary to maintain the concentration of penicillin in the blood and tissues continuously at

the maximum bactericidal level in order to attain recovery But, the truth of the matter is that optimum time dose relationships have not been worked out for all infections and we do not know whether the present day results can be improved by changing time dose relationships or not

Time Dose Relationship

There are two points of view concerning time dose schedules of penicillin, (1) intermittent treatment so spaced that there are periods of effective plasma concentrations separated by penicillin free intervals (2) intermittent or continuous injections of penicillin that will maintain an effective bactericidal plasma concentration for a sufficient period of time to completely inhibit the growth of organisms, plus the time required for the organisms to recover from the drug and effectively resume multiplication In other words one point of view is that penicillin should be present in the blood continuously, or at least for prolonged periods of time and the other view is that penicillin need be present in the blood only intermittently The difficulty in deciding how often and how much penicillin should be given resolves itself into determining what an effective plasma concentration should be and how long a period may elapse between injections before bacteria will begin to grow once again and cause relapse Only experience and experiments with various infections can provide the answers for all infections

In our own clinic Dr Weinstein has demonstrated that following the use of penicillin in children, 100,000 units every 8 hours penicillin is found in the blood for only two hours after injection i e, 6 hours out of the 24 hour period, and that streptococci disappear from the local lesions promptly within 24 to 48 hours Moreover, following the use of 300 000 units of penicillin by mouth every 8 hours similar good results were obtained but penicillin was detected in the blood for a longer period of time i e for 6 hours after each dose

It seems plain therefore that periods of effective concentrations separated by penicillin-free intervals are, in fact as effective as continuously maintained levels in the treatment of hemolytic streptococcic infections in children

In gonococcic infections we know that 98 per cent of patients can be cured with a single injection of 300 000 units in peanut oil and wax or with 50 000 units given in aqueous solution every 3 hours for 3

doses (total dosage 150 000 units) We have some evidence that as little as 17 500 units of procaine penicillin in oil is sufficient to cure 98 per cent of patients with gonorrhea

For pneumococcic lobar pneumonia it has been shown that 100 000 units given 3 times a day or 200 000 or 300 000 units given twice a day is sufficient for curing 95 per cent of patients

One of the reasons that there are such wide variations in the time dose schedules is due to the fact more penicillin is given in most infections than is necessary to obtain excellent results

In summing up the question of dosage then it can be said that the decision concerning the total daily dose of penicillin and the time interval between injections will depend upon the type and location of the infection the selection of the dosage form (i e oral aqueous solution penicillin in oil and wax or procaine penicillin in oil) and most important of all the response of the patient to treatment

We know that penicillin has been effective in many infections when it is given by intramuscular injection every 2 3 or 4 hours We know further that penicillin in oil and wax and procaine penicillin in oil or in aqueous suspension has been effective when given once daily Moreover when penicillin is given by mouth every 3 hours in 3 to 5 times that which is given parenterally it is effective Recently it has been shown that patients with lobar pneumonia may recover on either 200 000 or 300 000 units in aqueous solution given twice daily or following 100 000 units every 8 hours These observations certainly suggest that it is unnecessary to have penicillin present in the tissues constantly in order to obtain favorable results

The final decision concerning dosage must rest with the physician who is observing the response of the patient The trend of treatment has been to increase the amount of penicillin that is given by individual injection and to lengthen the time interval between injections

Penicillinase

It was early shown that *Escherichia coli* and certain other bacteria that are insensitive to penicillin produce a substance that inactivates penicillin To this substance has been given the name penicillinase Penicillinase can be prepared easily and its incorporation in culture media to inactivate penicillin present in the blood and exudates of patients under treatment with the drug has been suggested Studies

indicate that this procedure is of significant practical value in bacteriological work

Spink has observed an interesting phenomenon He has found that staphylococci that become resistant to penicillin in vivo during the treatment of infections with penicillin develop the ability to form penicillinase whereas staphylococci that are made resistant to penicillin in vitro do not form this substance This observation suggests the possibility that there is more than one mechanism whereby an organism may develop resistance to penicillin

Penicillin Sensitivity

A simple test for determining the sensitivity of any bacterial strain to penicillin has been described by Rammelkamp and Maxon Testing of strain sensitivity may be very useful in certain circumstances This test is particularly valuable in cases of subacute bacterial endocarditis due to non hemolytic streptococci that vary considerably in their sensitivity but it may be helpful also in any infection in which the patient does not respond to penicillin therapy in the manner expected

Bacterial Resistance Natural and Acquired

It is now well established that prolonged and repeated exposure of various bacteria to penicillin in vitro will select certain organisms that are increasingly resistant to its action Some strains of staphylococci are highly resistant to penicillin before they are ever exposed to it Other resistant strains emerge during treatment of patients It is a curious fact that resistant strains of gonococci pneumococci and group A hemolytic streptococci have not been encountered in human infections There have been some strains of non hemolytic streptococci that are naturally resistant to penicillin or become more resistant following treatment In general however penicillin failures have not been due to resistant organisms The widespread use of penicillin has not led to the production of a large number of penicillin resistant organisms The risk of producing such strains seems to be minimal

PHARMACOLOGY OF PENICILLIN

Absorption and Excretion

Solutions of the sodium or potassium salts of crystalline penicillin G are absorbed rapidly from the muscles The absorption of penicillin from these deposits in muscles can be delayed considerably by injecting these salts suspended in peanut oil and beeswax When procaine penicillin G in oil or in aqueous suspension is injected into the muscles its absorption is delayed so that penicillin continues to appear in the blood for 24 hours or longer following a single injection

When penicillin is given by mouth some may be destroyed by the gastric juice some fails to be absorbed by the intestine and some is destroyed in the large intestine Varying amounts are excreted in the urine following oral administration McDermott has demonstrated that when blood levels are compared following oral penicillin and parenteral injection of penicillin into the muscles it requires 3 to 5 times as much penicillin by mouth as when the penicillin is given intramuscularly

Penicillin is excreted rapidly in the urine and in the bile in higher concentrations than in the blood The drug has not been detected in the saliva tears pancreatic juice succus entericus or gastric juice of man

In order to delay the excretion of penicillin various methods have been devised The administration of para amino hippuric acid and caronamide partially blocks the excretion of penicillin by the kidney tubules Para amino hippuric acid must be given intravenously but caronamide can be given by mouth Caronamide has had the widest use When caronamide is given at least 4 grams every 4 hours are required to delay the excretion of penicillin in patients under 50 years of age In patients over 50 years of age a delay in excretion follows the use of 2 grams every 4 hours In patients in whom it is desirable and necessary to give large amounts of penicillin to control an infection such as occasionally occurs in bacterial endocarditis or in a resistant staphylococcic infection caronamide is a useful agent

Distribution in Body Fluids

The distribution of penicillin in the body after intramuscular or oral administration presents features that are of importance in the management of certain infections In normal persons when penicillin

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Topical therapy includes the injection of penicillin into several areas of the body including the subarachnoid space the pleural and abdominal cavities the joints the eye the paranasal sinuses and infected wounds It also includes the application of the drug to surface burns of limited extent and superficial infections of the skin

In selected cases topical therapy alone may be adequate to control an infection Workers in England particularly have carried out extensive studies of this form of penicillin therapy In many instances however topical therapy must be supplanted by systemic therapy This is particularly true whenever there is any significant extension of the infection beyond the walls immediately lining the infected cavity

For *intraspinal administration* the lumbar sac generally is used The diffusion of penicillin from this site throughout the subarachnoid space and ventricular system is adequate in most cases and there appears to be little need to administer the drug by way of the cisterna magna or through burr holes except in unusual circumstances Solutions containing 5 000 units per c c of physiological salt solution usually are employed for intrathecal therapy Dosages up to 0 000 units can be given safely in one injection and usually insure the maintenance of an adequate level of penicillin in the spinal fluid for 12 to 4 hours One injection a day may be sufficient until the infection has been controlled definitely It is recommended that an amount of spinal fluid equivalent to or greater than the volume of penicillin solution to be injected be withdrawn prior to each administration

For *intra articular injections* concentrations of 10 000 to 50 000 units per c c are employed and the injections are made once every 4 hours

In the treatment of *empyema* the common practice has been to inject 50 000 to 100 000 units daily or on alternate days The concentration employed is usually 2 000 units per c c but this may be varied depending on the size of the cavity Whatever pus or fluid is present should be aspirated if possible prior to each injection

For *injection into the anterior chamber of the eye* or for *topical administration by means of iontophoresis* or a *corneal bath* solutions containing 1 000 units per c c have been found to be safe and effective A similar solution can be used in the treatment of infections of the conjunctiva and cornea in the form of drops instilled into the conjunctival sac every or 3 hours

Instillation of penicillin *into the maxillary sinuses* is feasible through an indwelling catheter or long needle Experience with this form of

is administered in the usual therapeutic doses, no drug can be detected in the cerebrospinal fluid. In patients with purulent meningitis small amounts have been observed to pass into the spinal fluid. The concentrations that have been found have been low and have varied considerably in different patients. From the evidence that has been accumulated to date systemic administration alone is less effective in the treatment of bacterial meningitis unless massive doses are given (8 0 to 1 0 million units a day).

The passage of penicillin into the pleural and abdominal cavities and into joints is more satisfactory and levels approximating those present simultaneously in the blood have been reported. Again, however, clinical experience indicates that the systemic administration of penicillin frequently is not effective in controlling infections involving these sites.

The penetration of penicillin into the various parts of the eye is extremely poor. After intramuscular injections traces have been detected in the aqueous humor but those who have investigated the problem most thoroughly have concluded that topical application is essential to secure an adequate concentration of penicillin within the eye.

Methods of Administration

Several methods of administration that have proved to be effective are now in common use. The various methods may be grouped in three main categories, intermittent injections, topical applications, and oral administration.

In the group of methods in which *intermittent injections* are employed the *intramuscular* route is the one most commonly used. It is safe to say that more than 95 per cent of the penicillin being used today is administered by intramuscular injection. Clinical practice has established firmly the convenience and effectiveness of this method of administration for all types of infection. It has been shown that intramuscular injections are best tolerated in the buttocks and less well in the deltoid and the triceps muscles. When the volume of the individual dose is 3 cc or less repeated injections into the buttocks often can be tolerated for several weeks without too great discomfort. Penicillin is so extremely soluble that the concentration of solutions can be easily adjusted so that no more than this amount need be given at one time. In most clinics the intramuscular injections are given at 4 6 8 hour intervals throughout the day and night.

cision to use penicillin no choice is necessary between the various salts of penicillin. They are all effective and non toxic and they can be used interchangeably. Penicillin may be given parenterally by the intramuscular route or injected into the serous cavities the joints or the subarachnoid space or applied locally to wounds.

The route of choice is the intramuscular one. This may be carried out by intermittent injections. To delay absorption and to reduce the total number of intramuscular injections the sodium or potassium salts of penicillin G may be combined with beeswax and peanut oil or the procaine salt of penicillin G may be suspended in oil or in aqueous solution and injected once daily.

When penicillin is given by mouth it is well to remember that it requires at least 3 to 5 times as much as is given parenterally to obtain the same blood levels as might be expected after intramuscular injection. The minimum effective dose of penicillin by mouth has not been worked out for all infections.

Before starting treatment it is always desirable to know what organisms are involved in the infection. When this is not possible an attempt to establish an etiological diagnosis should be made as soon as possible.

PENICILLIN IN STAPHYLOCOCCIC INFECTIONS

There is no question but that penicillin is the most effective chemotherapeutic agent yet discovered for the treatment of staphylococcic infections regardless of their location. The commonest sites of infection are the bones, skin, subcutaneous tissues, infected wounds, lungs and pleura, joints, mastoid, urinary tract, endocardium and the meninges. Other sites are involved less often. All patients with staphylococci infections regardless of their location should receive treatment at once and it should be continued actively until all signs of infection have disappeared.

Bacteremia.—The results in the treatment of these infections associated with bacteremia have been most striking. The fatality rate can be reduced to within 10 to 15 per cent if treatment is started early and continued at the rate of 300 000 to 500 000 units a day until the infection is under control. In some cases 1 000 000 or more units a day may be required to control infection. Poor results are observed only when treatment has been started late in the course of the disease when the infection is an overwhelming one with signs of multiple abscesses in various organs.

therapy has not been sufficiently extensive to permit the formulation of any definite treatment schedules The instillation of a solution containing 1,000 units per c c every 8 hours has been effective in a few cases

For *topical application in infected wounds* of the soft tissues or bones concentrations varying from 250 to 10,000 units per c c have been used It is most convenient in such cases to insert into the depth of the wound a small rubber catheter which is left in place throughout treatment The wound edges should be approximated or the wound carefully packed so that the solution will remain in situ The interval between instillations can be varied from 3 to 12 hours depending on how quickly the fluid drains away or is absorbed

For *application to superficial burns and skin infections* penicillin is used most commonly in the form of wet dressings employing solutions of 250 units to 1 000 units per c c depending on the area being treated and the bacterial flora The drug has been applied also in powdered form and in ointments to such areas

Oral Penicillin—A recent study on the therapeutic effects of penicillin when given by mouth has been reported by Robinson Hush and Dowling They studied the results in 350 patients with a variety of infections and compared them with the results obtained in 600 patients with similar diseases who were treated by intermittent intramuscular injections The oral doses were approximately five times as great as the parenteral doses The results were comparable to those obtained with parenteral therapy in the case of pneumonia, streptococcic sore throat scarlet fever and otitis media They were less satisfactory in Vincent s stomatitis and poor in the case of bacterial endocarditis The results in the treatment of gonorrhea by the oral route have been reviewed by Meads and Finland They report favorable results in 85 per cent of patients and in their opinion it becomes necessary to give 600 000 units or more over a period of 7 hours Hypersensitivity reactions are less frequent than when penicillin is administered by other routes

CLINICAL USE OF PENICILLIN

The indications for the use of penicillin the route of administration the daily dosage and the duration of treatment depend on many factors that must be worked out in each case or in each group of cases Penicillin should be used as the drug of choice in the treatment of all infections caused by susceptible organisms (Table I) Once having made the de-

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or when there are signs of bacterial endocarditis or some complicating disease such as diabetes mellitus or gangrene of an extremity. Local lesions such as cavernous sinus thrombosis and meningitis also increase the fatality rate, but even in these cases the results are more favorable than those obtained with any other form of treatment.

It is a matter of common observation that patients with *Staphylococcus aureus* bacteremia may not show any appreciable improvement for several days after beginning treatment. It is not unusual, however, for patients to begin to show signs of improvement several days before the blood is cleared of organisms and a week or ten days before the temperature returns to normal. Treatment should be continued then until all signs of infection have subsided and until all the constitutional symptoms and signs have disappeared.

In some instances surgical drainage is a necessary adjunct to penicillin treatment. There are certain infections, however, in which a delay in surgical action may shorten the recovery period and result in less permanent dysfunction or disfigurement. For example, carbuncles respond exceedingly well to penicillin and surgical incision and drainage or incision is unnecessary except for the evacuation of obvious collections of pus. Continuous treatment for 10 to 14 days usually is sufficient to cause complete resolution of infection although the separation of slough and the epithelialization of denuded areas often has not been completed for another 1 to 3 weeks.

Acute Hematogenous Osteomyelitis.—When penicillin is started early in the course of acute osteomyelitis and is continued at the rate of 200 000 to 300 000 units a day, complete recovery commonly occurs without surgical drainage. When the process is associated with a soft tissue abscess or a suppurative arthritis surgical drainage is absolutely necessary in addition to systemic injections of penicillin. Under penicillin treatment alone the rapidity of clinical recovery and the extent of healing and repair of the damaged bone appear to surpass those of cases treated with surgical drainage. When suppurative arthritis is present surgical drainage is essential and penicillin should be injected locally into the joint once or twice a day. In all cases of acute osteomyelitis it is desirable to continue the treatment for at least 2 or 3 weeks and in severe cases with multiple bone lesions treatment for a longer period may be necessary.

Since the roentgenographic changes in the bone lag behind the clinical improvement too much reliance must not be placed on this sign

The clinical signs of recovery rather than the roentgen ray signs should be determining factors in deciding when treatment should be discontinued Not infrequently the destruction of bone is most extensive as judged by the x ray when it is obvious that the patient has recovered from the signs of acute infection Even when treatment has been stopped at this stage rapid repair of the bone with a striking return toward the normal architecture usually takes place within a few weeks or several months In occasional cases in which treatment is started early no signs of bone destruction ever develop in the roentgenograms

Excellent results have been reported in the treatment of osteomyelitis of the facial bones by Kirby and Hepp Infection of these bones commonly is followed either by serious intracranial complications or by death A number of recoveries following penicillin treatment are now recorded When sequestra are present surgical treatment along with penicillin is necessary for complete recovery

Chronic Osteomyelitis —The treatment of chronic osteomyelitis with penicillin has been most satisfactory when combined with surgical treatment Anderson Howard and Rammelkamp state that they are able to secure an arrest of the disease with the disappearance of all local and constitutional signs of active infection in 70 per cent of their patients with chronic osteomyelitis Prolonged treatment varying from 2 to 6 weeks is necessary in order to achieve the best results When sequestra are present it is necessary to remove them surgically in order to obtain satisfactory healing When relapses occur it is necessary to repeat the treatment The primary closure of wounds after sequestrectomy together with the local administration of penicillin into the cavity by means of a small catheter greatly shortens the recovery period Thick fibrous sinuses must be excised and all dead and necrotic tissue removed It must be reported that patients with chronic osteomyelitis receive the greatest benefit only when penicillin is combined with adequate surgical measures

Staphylococcus Aureus Pneumonia —Primary staphylococcic pneumonia as well as the cases that are secondary to some other disease such as epidemic influenza type A has responded well to penicillin In the absence of secondary foci of infection such as empyema pericarditis or areas of suppuration elsewhere recovery usually is complete without abscess formation in the lung within 1 to weeks In cases associated with bacteremia the blood may not be cleared for a period of to 3 days after penicillin is started Treatment should be continued for at least 7 to 14 days or longer depending on the clinical course In the cases of

metastatic staphylococcic pneumonia the treatment must be intense and in many instances must be carried on for a longer period of time i e 3 or 4 weeks depending on the clinical response of the patient If empyema develops, penicillin should be introduced directly into the thoracic cavity This is followed usually by a decrease or disappearance of fever and a marked lessening of the signs of intoxication In most cases, however the exudate does not become sterile, and thoracotomy is necessary to effect complete recovery

Staphylococcic Empyema—As in other types of empyema the prognosis of staphylococcus infection in patients under 40 who are treated within the first 2 weeks of the onset of their infection is very good In order to obtain the best results penicillin should be administered both systemically and intrapleurally Surgical drainage of the empyema is often a valuable adjunct measure It is not always necessary in order to effect recovery

Otitis Media and Mastoiditis—Otitis media due to staphylococcus responds in a remarkable manner following penicillin treatment Daily dose of 100,000 units for a period of 4 to 10 days usually is adequate In the case of mastoiditis of staphylococcus etiology there is no doubt but that penicillin may in many instances cause a complete regression of the lesion without surgical treatment of any kind In patients who have been treated with mastoidectomy penicillin is often responsible for complete recovery Daily dosage from which the best results were obtained was at least 100 000 units a day for a period of 7 to 14 days

Cavernous Sinus Thrombosis—Penicillin is an extremely effective agent in the treatment of cavernous sinus thrombosis and recovery results in a high percentage of cases even when serious complications are present Approximately 70 per cent of the patients recover and remain well following a course of penicillin alone Occasionally there is loss of vision of the involved eye or impaired vision following recovery Penicillin should be given in amounts of at least 100 000 to 500 000 units a day and continued for a period of 1 to 3 weeks depending upon the course of the disease

Lateral Sinus Thrombosis—In the treatment of lateral sinus thrombosis of staphylococcus etiology intensive treatment with penicillin systemically is indicated at once If meningitis is present, intrathecal therapy must be used as well The jugular vein on the infected side should be ligated if pulmonary infarction is a complication Mastoidectomy may be necessary in the treatment of the patient

Wound Infection—Staphylococcus is the commonest micro-organ

ism that contaminates wounds of all kinds Careful surgical management of all wounds is extremely important along with chemotherapy The dosage must be gauged with the location size of the wound and the response to treatment One to five hundred thousand units a day usually is indicated in most wound infections

Multiple Subcutaneous Abscesses—Multiple subcutaneous abscesses either acute or chronic respond extremely well to penicillin treatment In these cases the fever gradually subsides the organisms disappear from the draining sinuses within several weeks and complete healing follows within 3 to 4 weeks

Arthritis—Staphylococcic arthritis occurs most often following staphylococcic bacteremia In a few instances there is an associated osteomyelitis with extension of infection into the joints or trauma to the joints with secondary infection The results of penicillin treatment have been striking indeed from the point of view of recovery from infection and restoration of normal function The results of treatment can be improved by the combined use of systemic penicillin and injection of penicillin directly into the infected joint cavity When penicillin is given by both routes it is only seldom that surgical treatment of the infected joint is necessary At least 200 000 to 500 000 units a day should be administered intramuscularly and 50 000 units should be injected into the joints daily for a period of 2 to 3 weeks depending upon the course of the disease

Meningitis—Staphylococcic meningitis may be a part of generalized sepsis or it may follow an infection of the mastoid process or paranasal sinuses a skull fracture or an infected wound In about one third of the cases the portal of entry is unknown It affects all ages and is seen most often under the age of 5 years and over 20 years

Following penicillin intramuscularly and intrathecally it can be anticipated that at least 45 per cent of patients will recover Treatment should be started early in the course of the disease since most of the fatalities occur within the first week of the illness At least 500 000 units of penicillin should be given daily by the intramuscular route and 40 000 units of penicillin should be given daily intrathecally for a minimum period of three weeks Also all patients should receive sulfonamides at the same time since there is evidence that the simultaneous use of sulfonamides with penicillin improves the patients chances of recovery

Endocarditis—In order of frequency the staphylococcus causes endocarditis more often than any other organism except the nonhemolytic

streptococcus The patients may show an acute rapidly progressive disease or they may have a protracted course In the acute cases foci of infection may be found in many of the organs, and lesions in the heart valves are only one feature of a general septic infection When the disease runs a protracted or subacute course, then the infected focus will be confined to the heart valves until late in the course of the disease when a complicating meningitis may occur

All cases of staphylococcic bacteremia should be treated promptly in an attempt to prevent the localization of organisms on the heart valves and all patients with valvular heart disease with any form of staphylococcic infection should likewise be treated promptly In spite of treatment the fatality rate is still about 80 per cent, when dosage schedules are 300,000 units or less a day It is recommended therefore, that at least 500,000 units a day should be given and preferably 1,000 000 units a day for 4 to 8 weeks The factors that limit the outcome are the presence of associated lesions such as multiple abscesses brain abscess, meningitis pericarditis pneumonia, osteomyelitis and arthritis

Penicillin in Hemolytic Streptococcic Infections

Hemolytic streptococcal infections are much more sensitive to the action of penicillin than staphylococcic Local infection with or without bacteremia usually responds promptly to the administration of 100 000 to 500 000 units a day depending upon the location and severity of the infection In the case of most infections it is necessary to continue the treatment for at least 7 to 10 days in order to obtain the maximum benefits and prevent relapses

Acute Tonsillitis and Scarlet Fever—Following the use of penicillin in acute tonsillitis and scarlet fever, suppurative complications such as peritonsillar abscess, acute otitis media and acute suppurative lymphadenitis can be prevented Prompt treatment with 100 000 units of penicillin every hour by the intramuscular route or 150 000 units every 8 hours by mouth usually is followed by the disappearance of the fever and of the hemolytic streptococci from the throat within a period of 48 to 72 hours This treatment should be continued for a period of 5 to 7 days in order to prevent relapses of infection

Acute Otitis Media and Mastoiditis—Acute otitis media and mastoiditis respond very promptly to treatment In the case of mastoiditis it may be necessary to do a simple mastoidectomy to remove the necrotic

cells, closing the wound tightly except for a small catheter that is inserted into the cavity. Local treatment of 50,000 units a day to the cavity usually is followed by complete healing in four to seven days. Following operation, systemic treatment as well as local treatment should be continued. Early vigorous continued treatment is the most important feature to obtain successful results.

Meningitis.—Infection of the meninges by hemolytic streptococcus usually follows infection of the middle ear and mastoid process, paranasal sinuses or the upper respiratory tract and occasionally a metastatic or wound infection. In a few instances it is impossible to determine the portal of entry. Approximately 15 per cent of patients have an associated bacteremia. Thrombosis of the lateral sinuses or the cavernous sinuses may be present, and distant lesions such as arthritis and osteomyelitis may become complications. The vast majority of cases are observed between the ages of 1 and 10 years. At least 70 per cent of patients with hemolytic streptococcic meningitis recover following penicillin treatment. Systemic treatment should consist of at least 200 000 units a day and intrathecal injections should be at least 50 000 units a day for 7 to 14 days. Removal of foci of infection is important, and the combined use of penicillin and sulfadiazine is optional. The outlook is less favorable when there is associated lateral sinus or cavernous sinus thrombosis.

Endocarditis.—Infections of the heart valves with a hemolytic streptococcus follow infections of the throat or the uterus. Wound infections of the skin and tooth extraction are also sources of entry. The incidence of previous valvular disease in this type of endocarditis, that is bacterial endocarditis, is about 50 per cent. Approximately 50 per cent of patients recover following the exhibition of 300 000 to 500 000 units of penicillin daily for a period of 4 to 8 weeks. Factors that influence the outcome unfavorably are patients over the age of 40, those who receive small amounts of penicillin and those who have had the signs of infection for a month or longer before treatment is started. The prognosis is always better in patients who live long enough to obtain the full course of 4 to 8 weeks treatment.

Peritonitis.—Eighty per cent of patients with hemolytic streptococcus peritonitis recover following the use of penicillin. The minimum dose should be at least 500 000 units a day, given for a period of 7 to 14 days. The results have been striking in the treatment of this type of serous sac infection without instillation of penicillin into the peritoneal cavity.

Pneumonia and Empyema.—Adults with hemolytic streptococcus

pneumonia have shown striking improvement in 80 per cent of cases A minimum period of 7 days treatment is indicated in all of these infections, and the amount of penicillin should be 300 000 to 500 000 units a day In the treatment of empyema due to hemolytic streptococcus penicillin is effective when both systemic and intrapleural injections are made At least 50 000 to 100 000 units of penicillin should be injected daily into the pleural cavity after aspiration of pus Inasmuch as the results are always better following the systemic and topical treatment, penicillin should be given in amounts of 300 000 to 500 000 units intramuscularly a day for a period of 7 days or longer depending upon the clinical course of the disease

Puerperal Sepsis, Postabortal Sepsis—The first patient to be treated successfully with penicillin in the United States had hemolytic streptococcal puerperal sepsis that had been resistant to sulfonamides Subsequent experience has demonstrated that penicillin is an entirely satisfactory chemotherapeutic agent in the treatment of this type of infection Eighty per cent of patients have recovered completely following the use of the minimum amount of 200 000 units a day for 10 days or longer In approximately 50 per cent of cases the blood cultures are positive and there may be an associated pelvic abscess or thrombophlebitis of the portal vein All patients suspected of having this infection should be treated actively and promptly

Summary of Hemolytic Streptococcus Infections—In summary it can be said that hemolytic streptococcus infections occupy a position about midway between pneumococcus and staphylococcus infections in the susceptibility to penicillin A wide variety of anatomical lesions caused by this organism in different parts of the body have responded in a remarkable way The early recognition of the disease with active and vigorous treatment over a period of 1 to 3 weeks has been followed in many instances by extraordinarily favorable results The amount and duration of treatment naturally will depend on the location and the response of the patient to treatment

Anaerobic Streptococcic Infections

Anaerobic streptococcic infections have responded irregularly to penicillin owing to the fact that there is a wide variation in strain sensitivity to the drug In our own experience the sulfonamides are never effective in these cases Therefore penicillin deserves a trial in

all cases Infections due to these organisms are encountered most often following childbirth and abortion and they are commonly associated with thrombophlebitis of the pelvic veins They are also present in empyema meningitis osteomyelitis infections of wounds and the skin and subcutaneous tissues Improvement has occurred in 60 per cent of all cases The daily dose of penicillin should be at least 500 000 units or more, and treatment should be continued for at least three weeks

Penicillin in Subacute Bacterial Endocarditis

It is now known that when penicillin is given in amounts of 500 000 to 1 000 000 units per day for at least 4 to 6 weeks there is a clinical arrest of the disease in approximately 65 per cent of cases In a certain number of patients death occurs before adequate treatment as mentioned above has been completed Such deaths are due to the infection to embolism or to acute heart failure

When clinical arrest takes place the following sequence of events may be observed Within 24 to 72 hours after treatment is started the patients often lose many of the constitutional symptoms of infection The anorexia disappears the appetite improves and the patient becomes more interested in his surroundings The temperature is promptly reduced in some cases to within normal limits within the first week In others after the initial decrease in temperature the fever continues for 6 to 8 weeks as a low grade fever In a third group it goes down only after 2 to 3 weeks Prolonged fever after the beginning of treatment may be due to an infection by a relatively resistant organism or to a complication or to a continuing tissue reaction Once the temperature becomes normal there may be occasional recurrences due to embolic phenomena

Within 1 to 5 days after treatment the blood cultures generally become negative and remain so except for occasional instances when a transitory bacteremia and embolic phenomena occur Petechial hemorrhages may continue to occur for 6 to 8 weeks after treatment is completed and emboli may occur up to 2 months The spleen decreases in size the leukocytes decrease in number anemia improves and clubbing of the fingers may recede

As might be anticipated there are no changes in the signs of valvular disease and the renal lesions are not influenced favorably by treatment It is now well established that all these favorable results may be obtained

with penicillin alone and that no anticoagulant such as heparin is necessary Following a clinical arrest the patient may return to apparently normal health in that the symptoms and signs of infection are absent Some patients have a relapse or recurrence of their infection within 9 months to a year If relapse occurs, however, it is most frequent (80 per cent) within 2 to 8 weeks after treatment has been discontinued If relapse occurs then the patient should be retreated with a larger dose than the one used during the first course of treatment, and it should be continued for at least 8 weeks

Of the patients who recover from signs of infection and who show no signs of re-infection or relapse, at least 85 per cent will remain well at least for 1 to 4 years after treatment Ten per cent of patients may die of heart failure cerebral embolism or renal insufficiency Another group recover from their infection and survive with symptoms and signs of various grades of heart failure

In brief, penicillin without anticoagulants is the most effective form of treatment for subacute bacterial endocarditis The signs and symptoms of infection disappear, and many of the patients return to their state of health prior to the onset of infection Others have a relapse or recurrence of infection that often responds to a second course of treatment still others recover and have varying degrees of heart failure Finally some die, usually from heart failure, from cerebral embolism, renal insufficiency or all three

Penicillin in Gonococcic Infections

The gonococcus is of all organisms the most sensitive to the action of penicillin Mahoney's original observation that penicillin produces rapid and permanent cures in gonococcic infections has been widely confirmed At least 97 per cent of all gonococcic infections of the lower genital tract in either the male or the female are cured within 24 hours by the administration of 150 000 units of penicillin Those failing to respond to the first course usually respond promptly to a more intensive and prolonged treatment No cases of penicillin resistant gonorrhea have yet been encountered

Various schedules of treatment have been used including the injection of 50,000 units every 3 hours for 3 doses Clinical cures occur in a high percentage of cases from a single injection of 300 000 units when penicillin is suspended in beeswax and peanut oil, or when 100,000 units

of procaine penicillin in oil or aqueous suspension are given in a single dose Oral penicillin is also effective the dosage schedule being 100 000 units every 3 hours for 6 doses

Gonococcic ophthalmia responds promptly and favorably following the local instillation of penicillin into the conjunctival sac It is well in these cases to use systemic treatment as well Infections causing arthritis prostatitis salpingitis epididymitis and endocarditis require a more prolonged and more vigorous treatment In the case of gonococcic arthritis penicillin should be injected directly into the involved joint whenever this is feasible Early treatment in the course of this infection should greatly reduce all of the complications which may be of a chronic nature

Penicillin in Meningococcic Infections

Penicillin is as effective as the sulfonamides in the treatment of meningococcic meningitis Many strains of meningococci are highly susceptible to the action of penicillin while some are as resistant as strains of staphylococci The variation in the sensitivity of difficult strains of meningococci may explain in part the differences in the results of treatment that have been reported Meads Harris Semper and Finland recorded their results of treatment of meningococcic meningitis They found that neither the bacteriological nor the clinical signs of improvement were as rapid in patients treated with penicillin as in those treated with sulfonamides Furthermore several of their patients treated with penicillin eventually required sulfonamide therapy before they recovered The meningococci do not disappear from the cerebrospinal fluid so rapidly following penicillin treatment as is observed following sulfonamide therapy

Penicillin should be used in all cases of meningococcemia since the blood may be cleared with extremely small amounts

In fulminating cases of meningococcic infection penicillin should be combined with the sulfonamides All patients who are treated with sulfonamides alone and who fail to respond favorably within 4 to 48 hours should receive penicillin

Penicillin in Pneumococcic Infections

The pneumococcus is sensitive to relatively low concentrations of penicillin For that reason many of the pneumococcic infections have

responded promptly and strikingly. When patients with pneumococcic lobar pneumonia receive it, the outcome is extremely favorable. The fatality rate is less than 5 per cent. Tillett was among the first to demonstrate conclusively that both pneumococcic pneumonia and empyema respond very promptly following penicillin treatment. Meads, Harris and Finland recorded favorable results in cases of pneumococcic lobar pneumonia in which the sulfonamides previously had failed to control the infection. They tell us that penicillin was equally effective in the patients who had received it alone, and in those who had failed to respond to the sulfonamides.

The following comments with respect to the treatment of pneumococcic pneumonia with penicillin are in order. When patients are treated early in the course of their disease, i.e., within the first 24 to 48 hours, usually there is a decrease in the temperature and pulse rate within 1 or 2 days, and preceding these objective signs, patients often express the opinion that they feel improved subjectively. Bacteremia, if present, disappears promptly, usually following the first injection, and purulent complications developing for the first time following the use of penicillin are exceedingly uncommon. They were not noted by Meads and his associates in any of their cases.

The dosage and duration of treatment vary from one patient to another depending on the clinical course, the severity of the infection and the route of administration of the penicillin. In some of the mild cases without bacteremia patients have recovered following 60 000 to 80 000 units a day for 2 days. This dosage schedule merely shows how little penicillin is needed in some cases. It is not recommended as a dosage schedule for most patients.

Accumulated experience indicates that it is sound practice to treat patients with lobar pneumonia with one injection of 100 000 units of aqueous sodium or potassium penicillin every 6 or 8 hours throughout the day or with 300 000 units of aqueous penicillin every 12 hours. Other variations in dosage schedule that have been effective are one daily injection of 300 000 units of penicillin in oil and wax or one daily injection of 300 000 units of procaine penicillin in oil or in aqueous suspension. When the patient fails to respond promptly to any of these dosage schedules that are elected, then the total daily dose may be increased and the time interval between injections shortened. It is well to continue treatment for at least 2 or 3 days after the temperature has reached normal in order to avoid relapses which may recur, if treatment is stopped abruptly after the first 48 to 72 hours.

When penicillin is given by mouth for the treatment of lobar pneumonia then 75 000 units every 3 hours (600 000) has been shown to be an adequate dose Here again treatment should be continued for 48 to 72 hours after the temperature becomes normal

Inasmuch as sulfadiazine and penicillin are both effective agents in the treatment of pneumococcic lobar pneumonia the question is frequently raised whether both agents should be used simultaneously and if not which drug is the one of choice In general it can be said that nothing is gained by giving both penicillin and sulfadiazine to patients with uncomplicated pneumococcus pneumonia Of the two agents it is generally agreed that penicillin is the drug of choice in all patients It should be started at once If sulfonamides have been started and the patient fails to respond favorably after 24 hours of treatment then penicillin should be substituted

Pneumococcic Empyema —Infection of the pleural cavity following pneumonia can be controlled frequently without thoracotomy by aspiration of the pus and by injecting penicillin directly into the cavity every 24 hours Systemic treatment should be continued also since the incidence of recovery is approximately twice as high with combined treatment as it is with systemic treatment alone or with intrapleural treatment alone Treatment should be continued for a minimum period of 2 weeks unless all signs of infection disappear before that time In some it is necessary to continue treatment for 4 to 6 weeks The minimum amount injected into the pleural cavity for optimum results is 100 000 units The solutions of penicillin should contain 10 000 units per c c They should be injected directly into the pleural cavity Irrigation of the cavity with penicillin is ineffective

Surgical treatment may be necessary when it is impossible to aspirate all of the pus or when the pus becomes loculated If it is necessary to drain the pleura surgically systemic and local treatment should be continued following the drainage

At least 75 to 80 per cent of patients recover on systemic treatment aspiration of pus and local instillation of penicillin into the cavity

Pneumococcic Meningitis —Pneumococcic meningitis always is a serious disease and before the days of the sulfonamides it was invariably fatal At the present time between 50 and 70 per cent of patients recover following the use of penicillin when it is used systemically and intrathecally There is evidence in small groups of cases that the combination of sulfadiazine by mouth and penicillin systemically and intrathecally is more effective than when either drug is used alone

One of the reasons that pneumococcic meningitis is such a serious disease is that it is frequently a metastatic lesion following pneumococcic lobar pneumonia with or without an associated bacterial endocarditis In other cases it occurs in elderly people or in those who have had cranio cerebral injuries suppurative mastoiditis or suppurative sinusitis of the ethmoid or sphenoid cells It commonly tends to produce hydrocephalus and encephalitis which may lead subsequently to cerebral atrophy and profound neuropsychiatric disturbances

The best results of treatment reported so far followed a combination of intrathecal and intramuscular penicillin A factor aside from the chemotherapy that influenced the outcome was the drainage of a focus of infection i e mastoiditis or sinus thrombosis if they were present In some reports the use of penicillin and sulfonamides has reduced the fatality rate below that of penicillin alone

In the 537 cases reported to the Committee on Chemotherapy of the National Research Committee the recovery rate was 51 per cent when systemic and intrathecal injections were used When systemic treatment alone was used then only 34 per cent recovered and when intrathecal treatment was used alone then only 32 per cent recovered Unfavorable factors were patients under the age of 2 years and over 40 bacteremia, duration of infection more than 7 days before starting treatment, associated brain abscess, encephalitis pneumonia or endocarditis

There is always considerable discussion concerning the advisability of injecting penicillin intrathecally Arguments have been advanced that it is unnecessary and that the recovery rate is as high when penicillin is given systemically without intrathecal therapy as it is when penicillin is given by both routes This is not in agreement with the results that were reported to us by many physicians, and which we have mentioned above The possibility exists however that if massive doses of penicillin are given every 2 or 3 hours i e 1 000 000 units or more are given regularly every three hours the recovery rate will increase on systemic treatment alone This is a most important problem and one that is receiving increasing attention For the present, however it would appear that it is well to treat all patients with pneumococcic meningitis with systemic and intrathecal penicillin and sulfadiazine by mouth The minimum daily amount of penicillin systemically should be 500 000 units and the maximum intrathecal dose should be 30 000 units daily If it is decided that penicillin should be given only by the systemic route then 1 000 000 units every 3 hours should be tried All demonstrable foci of infection should be drained

Pneumococcic Endocarditis — This disorder usually follows pneumonia or an infection of the middle ear or mastoid process About 15 per cent of patients develop endocarditis without any obvious portal of entry Before penicillin practically all patients died Now at least 40 per cent recover The minimum daily dose should be 500 000 units for a period of 4 weeks Unfavorable factors are an associated meningitis congestive heart failure cerebral embolism and renal insufficiency Early diagnosis is important but it may be difficult since at least 80 per cent of all patients develop infection on previously normal heart valves The presence of a persistent bacteremia that is otherwise unexplained or that is present following the regression of pneumonia is an important sign that arouses one s suspicion Patients under 30 years of age and without meningitis may be expected to show a higher rate of recovery than those over 30 with or without meningitis

Miscellaneous Pneumococcic Infections — Aside from pneumonia empyema meningitis and endocarditis a great many patients with pneumococcic infection of the joints pericardium peritoneum the middle ear and mastoid process have been treated with penicillin The results are far superior to any other forms of treatment Patients with middle ear and mastoid infection respond promptly and permanently Ninety per cent of patients with peritonitis have recovered two-thirds of the patients with pericarditis and three fourths of the patients with arthritis recover

In brief penicillin has been an extremely potent agent in the treatment of pneumococcic infection and should be used early in the course of all cases

Penicillin in Clostridial Infections

The clostridia are sensitive to the action of penicillin both in vitro and in clinical infections In war wounds in which gas gangrene developed the fatality rate was reduced when penicillin was combined with adequate surgical removal of all necrotic and devitalized tissue Jeffrey and Thomson recorded a fatality rate of 36.4 per cent in 33 cases of gas gangrene treated with penicillin

They emphasize as do all other physicians who have had experience with this disease that the adequate surgical removal of all necrotic and devitalized tissue is the most important therapeutic procedure in the management of gas gangrene Five of the patients reported by Jeffrey and Thomson were seen late in the course of the disease, when surgical

treatment was impossible All of these patients died in spite of treatment with penicillin Jeffrey and Thomson recommended a dose of 15,000 units every 3 hours for 3 to 4 days in all cases in which all the infected tissue can be removed surgically In cases, where this is not possible it is desirable to continue treatment for 5 to 10 days They also recommend the concomitant use of antitoxin They express the opinion that early and adequate surgery aided by penicillin and antitoxin will reduce the fatality rate in gas gangrene following battle casualties Cutler and Sandusky treated 7 patients with gas gangrene, 6 recovered In 5 cases gas gangrene developed while the patients were receiving penicillin as a prophylactic measure Following excision of diseased tissue all the patients recovered In a word it appears that penicillin should be used as an adjuvant to good surgery and along with antitoxin in the treatment of all cases of gas gangrene

A few cases of tetanus have been treated with penicillin and antitoxin but the group is entirely too small to assess the role that penicillin has played in recovery

In the civilian treated cases of clostridia infection reported to the Committee on Chemotherapy it was clearly established that penicillin therapy was effective The prompt recognition of the infection and a minimum daily dose of 200 000 to 500 000 units a day for at least 21 days are factors that influence recovery At least 75 to 80 per cent of all patients recovered The results were striking in both infections of the skin and subcutaneous tissues as well as in infection of the muscles Occasional cases of pelvic abscess empyema infected compound fracture cholangitis lung abscess orbital abscess and parotid abscess due to this group of organisms also recovered

All patients with clostridial infection then should receive penicillin Surgical treatment and sulfadiazine may also be of added benefit

Penicillin in Syphilis

In October 1943 Mahoney and his associates reported on the favorable action of penicillin in the treatment of early syphilis Following this report intensive studies of the treatment of early congenital and late syphilis have been carried out by a large group of clinics cooperating with the Penicillin Panel on Venereal Diseases of the National Research Council The original investigations were supported in large part by the Office of Scientific Research and Development, and they have been

continued with the support of the United States Public Health Service Thousands of patients have been treated and followed most carefully Periodic reports of the study group have appeared from time to time Moore s excellent monograph on Penicillin in Syphilis sums up the results up to 1946 Recent publications by the Study Section National Institute of Health on the status of penicillin in the treatment of syphilis as a report to the Council on Pharmacy and Chemistry of the American Medical Association outline the present concepts of treatment and make the following recommendations

Penicillin in Early Syphilis —It is recommended for the present that only crystalline penicillin G in aqueous solution be used for the treatment of all forms of syphilis early and late

The following points have emerged from the combined study The treatment schedule for early syphilis (primary and secondary) should be a total dose of 4 800 000 units given in divided doses of 50 000 units every hours day and night for 96 injections i e for 8 days This form of treatment demands hospitalization The failure rate at the end of one year following this schedule has varied from 3 5 to 10 per cent A high proportion of patients so treated remain symptom free for periods varying up to 18 months and become and remain sero negative The incidence of neuro relapse or of abnormal spinal fluids in patients treated by the schedule described is extraordinarily low and averages only 1 to per cent The critical period for the development of clinical or serological relapse is between the fourth and ninth months after treatment Relapses or reinfections have been observed as early as 4 weeks and/or as late as 3 years after treatment The results have been slightly better in infections of short duration (sero negative primary syphilis) than in those of longer standing (sero positive primary or secondary syphilis) When patients are retreated with penicillin alone following relapse after original treatment and regardless of the total retreatment dose failure rates are substantially higher than in patients treated for the first time

Early syphilis that is treatment resistant (with persistent dark field positive lesions) after previous chemotherapy with arsenic and bismuth compounds may be successfully treated with penicillin administered on the same schedule as for previously untreated early syphilis

If it is decided to treat patients in the office or on an ambulatory basis then crystalline penicillin G in oil and wax or crystalline procaine penicillin in aqueous suspension or in oil may be used The total dose recommended is 6 000 000 units given intramuscularly in divided doses of 600 000 units a day for 10 days It should be pointed out that at the

time of writing there is no specific information concerning the clinical results of using crystalline procaine penicillin G in aqueous solution or in oil nor is there any specific information concerning the use of crystalline penicillin G in oil and wax that is comparable to the study that was made with amorphous penicillin in oil and wax There is no good reason for believing however that procaine penicillin in oil or in aqueous solution or crystalline penicillin G in oil and wax will be any less effective than amorphous penicillin in oil and wax

Local pain and allergic reactions are slightly more frequent after penicillin in oil and wax than after aqueous solutions of the antibiotic

Retreatment of Penicillin Failures—When clinical relapse or reinfection or serological relapse occur following an initial course of penicillin consideration should be given to the use of a retreatment course consisting of penicillin and heavy metal treatment The heavy metal treatment should consist of 600 mgm of oxophenarsine hydrochloride given every other day in 10 intravenous injections of 60 mgm each over a total of 19 days and 2 000 mgm of bismuth subsalicylate in oil given every 5 to 7 days in 10 intramuscular injections of 200 mgm each (of the salicylate not of bismuth metal) over a total period of 50 to 70 days It should be recognized that arsenic and bismuth in the doses mentioned increase the risk of serious reaction and rarely, death from treatment The anticipated mortality rate has been about 1 in 30,000

Latent Syphilis—It is recommended that penicillin should be used in the same dosage schedule for the treatment of latent syphilis as is commonly employed in the treatment of early syphilis

Benign Late Syphilis—The immediate results in the penicillin treatment of benign late syphilis include cutaneous mucocutaneous osseous and hepatic lesions of benign late gummatous syphilis appear to be as good as with arsenic and bismuth therapy The total dosage recommended is 2 000 000 to 4 800,000 or more units of penicillin given over a period of 7½ to 8 days

Cardiovascular Syphilis—If penicillin is used in the treatment of cardiovascular syphilis the total dosage should be large that is 5 000 000 or more units and the individual dose relatively small 25 000 to 40 000 units The duration of treatment is prolonged to 15 or more days It should be remembered that Herxheimer reaction or therapeutic shock cannot be avoided in early syphilis by initiating penicillin treatment in extremely small doses Since this may also be true in cardiovascular syphilis and since therapeutic shock in such cases may have drastic results it has been suggested that in syphilitic aortitis with aortic regurgi

tation or vascular aneurysm or obvious or masked coronary or myocardial disease it may be advisable to withhold penicillin treatment altogether or at least until after preparatory treatment of heavy metals is given

Ocular Syphilis, Syphilitic Iritis—The use of penicillin is rapidly effective in the treatment of this disease The time and dosage schedule is similar to those employed for early syphilis Interstitial keratitis has not responded nearly so well as syphilitic iritis and indeed it is stated to be of uncertain value even if total doses of 4 000 000 to 10 000 000 units are employed Less than half of the infections respond promptly Fever therapy artificial malaria typhoid vaccine or other means combined with arsenic and bismuth therapy is recommended when acute inflammation and corneal infiltration does not respond promptly to penicillin therapy

Syphilitic Primary Optic Atrophy—These cases should be treated with fever preferably malaria At present the effectiveness of penicillin in primary optic atrophy has not been determined

Neurosyphilis—In general it can be said that a total of 4 000 000 to 10 000 000 units of penicillin alone in aqueous solution exhibited over a period of 7½ to [illegible] days is suitable as the initial course of treatment for patients with early or late asymptomatic neurosyphilis gumma of the brain or cord acute syphilitic meningitis profuse meningovascular neurosyphilis and vascular neurosyphilis When neurosyphilis entailing a serious threat to life or vital function is present that is dementia paralytica taboparesis primary optic atrophy nerve deafness late syphilis nonparetic syphilitic epilepsy and Erb s spinal spastic paraplegia it is recommended that both penicillin and fever therapy be given unless the latter is contraindicated In these cases a total of 10 000 000 to 20 000 000 units of penicillin administered over a period of 1[illegible] to 20 days accompanied by induced malaria is advisable

The Prevention of Prenatal Syphilis—It has been ascertained that penicillin has been nearly 100 per cent effective in the prevention of prenatal syphilis It should be given in all cases of maternal early syphilis since it is equally effective in protecting the fetus regardless of the trimester of pregnancy in which the treatment is given that is up to the eighth month of pregnancy Penicillin in aqueous solution is slightly superior to the suspension in oil and wax and the dosage schedules that have been used most successfully have 4 800 000 to 6 000 000 units of penicillin in aqueous solution administered at [illegible] to 3 hourly intervals over a period of 8 to 15 days Once penicillin treatment has been completed the mother must be followed clinically and with quantitatively titered serological tests at least as often as once a month until delivery

After delivery follow-up examination is based upon the stage of the mother's infection Retreatment with penicillin should be carried out during pregnancy if there is evidence of clinical or serological relapse or if the mother has been untreated previously or inadequately treated for syphilis of less than 4 years duration and the original maternal serological titer does not significantly decline within 3 months after treatment The infant must be followed afterward for a minimum period of 4 months by repeated physical examinations quantitatively titer blood serological tests practically every two weeks and roentgenograms of the long bones taken at the first and sixth weeks of life

Infantile Congenital Syphilis—Penicillin in aqueous solution should be given every two to three hours day and night in 60 to 120 equal doses of 20 000 to 40 000 units/kg for a period of 8 to 15 days This is the most satisfactory treatment of congenital syphilis in children under 2 years of age The incidence of clinical and serological relapse is less than 3 per cent The fatality rate during and after treatment has varied from 11 to 13 per cent but there is no evidence that any of the deaths were due to the penicillin

Late Congenital Syphilis—The results of treatment in this form of syphilis have been similar to that of those patients with analogous manifestation of the acquired disease It cannot be stated at present whether penicillin will arrest permanently the progression of late or latent congenital syphilitic infection The dosage schedules are the same as those recommended for other forms of late syphilis

Reactions Following Penicillin Treatment in Patients with Syphilis—The Jarisch-Herxheimer reaction is common in the treatment of all types of syphilis with penicillin Fever, with or without exacerbation of mucocutaneous or ocular lesions have appeared within 12 hours after starting treatment and lasting 24 hours in approximately 50 per cent of patients It has been suggested that initially very small, gradually increasing doses of penicillin may be advisable for patients with late syphilis among whom therapeutic shock is a potential danger This includes cardiovascular syphilis and neurosyphilis

The use of penicillin in the treatment of syphilis is discussed also by Tucker in Chapt XXVIII—4 Part II, Vol V of Oxford Medicine

Penicillin in Miscellaneous Infections

Actinomycosis—Most strains of actinomycoses are moderately sensitive to penicillin in vitro and many patients with actinomycosis have

been treated with marked improvement Altemeier has obtained very striking results in a number of patients when penicillin and sulfadiazine are combined When it is possible to excise infected tissues surgically this should be done but this procedure should be preceded and followed by penicillin treatment It is a striking fact that when the sinuses are superinfected with staphylococci these organisms disappear promptly and the sinuses may heal completely Recurrences in such cases are not unusual The most favorable results have been observed in facial actinomycosis and in actinomycosis of bone The cases of pulmonary and generalized actinomycosis respond the least well The minimum period of treatment should be at least 4 weeks and the minimum daily dosage should be 300 000 to 500 000 units In general it can be expected that at least 80 per cent of patients will show striking improvement following treatment

Anthrax—Anthrax responds in a striking manner to penicillin and it is the drug of choice in this disease Patients with this infection also recover following streptomycin Murphy LaBoccetta Lockwood and Weinstein and Oliver have reported on the successful use of penicillin in cutaneous anthrax with and without bacteremia The minimum dose for the average case of uncomplicated anthrax is 100 000 units daily for 4 to 7 days

When bacteremia is present or when there is massive edema of the infected parts then the treatment must be more intensive and it must be continued for at least 7 to 14 days In the cases of localized infections of the skin the organisms disappear promptly from the lesions and it is unnecessary to use surgical excision or any local injections of serum or other substances about the lesion

Rat bite Fever—The two causative agents of rat bite fever *Spirillum minus* and *Streptobacillus moniliformis* are both sensitive to penicillin in vitro A few clinical cases of infection due to *Streptobacillus moniliformis* have been treated with favorable results At least the course of the disease is definitely shortened

Weil's Disease—Experimental infections of *L icterohaemorrhagiae* in guinea pigs and in mice may be influenced when penicillin is administered within 4 to 48 hours after infection has been induced Once the infection has become established and clinical symptoms have appeared there is little or no evidence to show that the course of the disease has been changed Patterson reports 6 cases of Weil's disease treated with penicillin All the patients recovered and it was his opinion that on

After delivery follow-up examination is based upon the stage of the mother's infection. Retreatment with penicillin should be carried out during pregnancy, if there is evidence of clinical or serological relapse, or if the mother has been untreated previously or inadequately treated for syphilis of less than 4 years duration and the original maternal serological titer does not significantly decline within 3 months after treatment. The infant must be followed afterward for a minimum period of 4 months by repeated physical examinations, quantitatively titer blood serological tests practically every two weeks and roentgenograms of the long bones taken at the first and sixth weeks of life.

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Late Congenital Syphilis.—The results of treatment in this form of syphilis have been similar to that of those patients with analagous manifestation of the acquired disease. It cannot be stated at present whether penicillin will arrest permanently the progression of late or latent congenital syphilitic infection. The dosage schedules are the same as those recommended for other forms of late syphilis.

Reactions Following Penicillin Treatment in Patients with Syphilis.—The Jarisch-Herxheimer reaction is common in the treatment of all types of syphilis with penicillin. Fever with or without exacerbation of mucocutaneous or ocular lesions, have appeared within 12 hours after starting treatment and lasting 24 hours in approximately 50 per cent of patients. It has been suggested that initially very small gradually increasing doses of penicillin may be advisable for patients with late syphilis among whom therapeutic shock is a potential danger. This includes cardiovascular syphilis and neurosyphilis.

The use of penicillin in the treatment of syphilis is discussed also by Tucker in Chapt. XXVIII—4, Part II, Vol. V of Oxford Medicine.

Penicillin in Miscellaneous Infections

Actinomycosis.—Most strains of actinomycoses are moderately sensitive to penicillin in vitro and many patients with actinomycosis have

treated with penicillin and antitoxin the organisms disappear from the throat sooner than when antitoxin is given alone Also the carrier state can be eliminated in about 85 per cent of cases when 300 000 units are given daily for at least 10 to 14 days

Mixed Bacterial Infections—The effect of penicillin in infections in which the bacterial flora is mixed some of the infecting organisms being sensitive to penicillin and others resistant to it appears to depend on the relative importance of the penicillin sensitive organisms in initiating and maintaining the infection For those in which the penicillin-sensitive organisms are largely responsible for the pathological process penicillin therapy may be of great value Examples of this are encountered frequently in infected wounds and chronic osteomyelitis In such cases penicillin sensitive organisms such as staphylococci and hemolytic streptococci usually are responsible for the active infection The penicillin resistant gram negative bacilli that are also present appear to act chiefly as contaminants When penicillin is administered the penicillin sensitive organisms usually disappear the infection subsides and healing progresses even though some gram negative pus may continue to form for a longer or shorter period of time

In other mixed infections such as peritonitis following a ruptured appendix or perforation of the intestine it frequently appears that the penicillin resistant organisms are chiefly responsible for the resulting infection and the use of penicillin oftener than not fails to effect improvement

In mixed infections of the urinary tract a very similar situation obtains It is not uncommon in such cases for the original symptoms to persist despite the disappearance of the penicillin sensitive organisms

The use of other antibiotics along with penicillin in the treatment of mixed infections is often most helpful Streptomycin the sulfonamides and bacitracin may be employed along with penicillin when the infection is a mixed one and it is difficult to decide the role of the various organisms in infection It is especially important in cases of peritonitis due to a mixed infection with intestinal bacteria

Thus it can be seen that no all inclusive generalizations can be made concerning the effectiveness of penicillin in mixed infections Each case must be evaluated separately and caution must be exercised in not relying too heavily on the use of penicillin to the exclusion of other therapeutic measures of established value

the average the treated patients were not as ill as those who received no specific treatment

Yaws—A number of reports concerning the effect of penicillin in yaws have appeared Dwinelle, Sheldon Rein and Steinberg have reported on the analysis of 500 patients Various dosage schedules were used One group of patients received 40 000 units every 3 hours for 30 injections Another group received 2 injections of penicillin in oil and wax 24 hours apart with the total dose varying from 600 000 units in children to 1,200,000 units in adults A third group received the same dose as group two, but all of the treatment was given in one day, two injections were given either 10 or 12 hours apart

The use of penicillin by these dosage schedules controlled the cutaneous lesions and prevented spread of infection from local lesions The patients who received 4 days of treatment, improved more often than those who were treated for 1 or 2 days but satisfactory progress of the disease was almost identical in all three groups

From this study it would appear that at least 90 per cent of patients will show satisfactory progress within 10 to 12 months after treatment Penicillin is said to be the present day drug of choice in the treatment of yaws

Relapsing Fever—The use of penicillin in the treatment of tick borne relapsing fever has been discussed by Fischer who reports a favorable response of a patient with relapsing fever who received 650,000 units In louse borne relapsing fever Greaves, Geyon and Alston report favorable results following penicillin The results are as effective as those following neoarsphenamine, and it is recommended for use in all cases with jaundice The dosage schedule employed was 30 000 units every 3 hours for 48 hours It is plain that penicillin or neoarsphenamine should be used in the treatment of all cases of relapsing fever

Erysipeloid—Infections due to *Erysipelothrix rhusiopathicae* have responded to penicillin The results in the case report by Ehrlich were impressive

Diphtheria—Penicillin is active in vitro against *Corynebacterium diphtheriae* Penicillin should never be used alone for the treatment of diphtheria Antitoxin should be used in all cases There is no evidence that penicillin alone or in combination with diphtheria antitoxin influences the course of the disease or prevents complications Weinstein has demonstrated however that, when patients with acute diphtheria are

desirable They recommend crystalline penicillin with physiological saline as a diluent The daily dosage recommended varies from 150 000 to 500 000 units although as much as 1 000 000 units have been employed In general it can be said that the aerosol method of treating these patients constitutes a technic which may be added to other forms of therapy

In local infections due to susceptible organisms penicillin has proved to be an extremely valuable agent

Penicillin as a Prophylactic Agent

Penicillin has been used to prevent invasive infections when the normal defense mechanism of the body is ruptured such as occurs following dental extraction surgical removal of a lobe of a lung or operation in an infected field Likewise it has been employed to prevent streptococcic sore throat in rheumatic subjects

Prophylactic penicillin has proved to be very effective in preventing infection following thoracotomy for exploratory surgical procedures or for esophagectomy also for the prevention of empyema following lobectomy or pneumonectomy although in the case of lobectomy the incidence of infection was moderately high when bronchopleural fistulae developed

As a prophylactic measure in preventing infection following operations *on bones and joints highly favorable results have been obtained* Infection has been prevented in 80 per cent of compound fractures and when infection has recurred the organisms present have been gram negative bacteria or occasional cases of staphylococcus infections All infections have remained localized and no cases of generalized infection have been reported

To reduce the incidence of infection in patients who require skin grafting or to facilitate successful grafting in the presence of infection or contamination penicillin has been found to be effective

In an attempt to reduce the number of cases of bacteremia following tooth extraction in patients with rheumatic heart disease or previous attacks of subacute bacterial endocarditis, penicillin has been used with success Various dosage schedules have been employed including 50 000 units [illegible]0 minutes prior to tooth extraction as a single injection or 50 000 units intramuscularly every [illegible] hours for 1[illegible] doses prior to extraction

Penicillin in Medical and Surgical Specialties

Penicillin has been adapted to the problems that are peculiar to various medical specialties. Infections of the conjunctiva and cornea, as a rule, respond well to local treatment, when the infecting organism is susceptible to the action of penicillin. The drug may be administered locally in solution or in an ointment. Infections of the internal structures of the eye are more difficult to treat because of the poor penetration of penicillin into these structures. Special methods for administration such as iontophoresis, the use of a corneal bath or direct injection of the drug into the anterior chamber of the eye usually are necessary.

Penicillin has been used with a high degree of success in the management of acute and chronic otitis media, acute mastoiditis and acute labyrinthitis. When the infection organisms are sensitive to penicillin, excellent results have been obtained. In selected cases penicillin alone may be successful; in other cases surgical procedures must be employed also.

The local use of penicillin postoperatively in patients with acute mastoiditis now permits the safe primary closure of incisions and greatly shortens the recovery period. Penicillin has been most useful in the treatment of some of the more serious complications of infections of the nose and throat and in chronic suppurative maxillary sinusitis.

In the field of plastic surgery Hirshfeld and his associates have reported that the systemic administration of penicillin greatly increases the percentage of successful skin grafts applied to infected surfaces.

The treatment of various infections of the skin with topical applications of penicillin in solution and in an ointment base has yielded excellent results in impetigo and in blepharitis. The immediate response of patients with sycosis barbae is striking, but a marked tendency to early relapse is often observed. The results in chronic eczema with secondary infection and in acne are irregular and inconclusive. Many observations indicate that penicillin therapy is not effective in psoriasis, herpes labialis and pemphigus vulgaris.

Gingivitis and stomatitis caused by Vincent's organism have been treated effectively by the use of penicillin pastilles.

The treatment of bronchiectasis, chronic bronchitis and lung abscess due to mixed infections with penicillin by inhalation has been reviewed by Garthwaite, Barach, Levenson and Rader. It is the opinion of these physicians that high concentrations of penicillin are needed locally for the control of many of these infections so that aerosol treatment is

desirable They recommend crystalline penicillin with physiological saline as a diluent The daily dosage recommended varies from 150 000 to 500 000 units although as much as 1 000 000 units have been employed In general it can be said that the aerosol method of treating these patients constitutes a technic which may be added to other forms of therapy

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Diseases in Which Penicillin Is Not Effective

The early clinical studies with penicillin were confined to the treatment of infections caused by organisms known to be sensitive to the action of penicillin

TABLE III

All gram negative bacillary infections	Ulcerative colitis
Tuberculosis	Coccidioidomycosis
Atypical pneumonia of unknown etiology	Malaria
Histoplasmosis	Poliomyelitis
Toxoplasmosis	Nonspecific iritis
Acute rheumatic fever	Nonspecific uveitis
Diffuse lupus erythematosis	Blastomycosis
Infectious mononucleosis	Moniliasis
Pemphigus	Virus infections
Hodgkin's disease	Cancer
Leukemia, acute and chronic	Rheumatoid arthritis
	Granuloma inguinale

It was only natural that when penicillin became available in large quantities attempts should be made to treat a wide variety of diseases of known and unknown etiology for which there was no laboratory evidence that the use of penicillin would be beneficial In most such diseases clinical experience quickly demonstrated that penicillin was of no value In Table III are listed some of the most important diseases in which penicillin therapy has been shown by clinical trial to be ineffective Only when these diseases are complicated by secondary infections caused by organisms susceptible to the drug, may penicillin therapy be of benefit

Reactions to Penicillin

One of the extraordinary features about penicillin is that it is a non toxic drug Reactions due to the action of penicillin upon tissues are exceedingly rare When excessive amounts of penicillin are injected into the subarachnoid space then convulsions are likely to occur With the use of therapeutic doses i e, less than 50 000 units per injection, con

vulsions are very rare indeed and in our own experience we have never seen such a reaction

The common forms of reaction are due to hypersensitivity to the penicillin itself Following intramuscular injection the types of reaction that are observed in 1 5 to 5 percent of patients consist of fever skin eruptions edema of the skin subcutaneous tissues and mucous membranes and arthralgias This type of reaction which resembles serum sickness in its clinical features may last from 1 to 3 weeks It causes extreme discomfort from itching and burning of the skin and sometimes from pains in the joints In general it is desirable to discontinue the penicillin and to treat the disorders with benadryl or pyribenzamine or small doses of epinephrine if necessary and with the local application of lotions for the relief of itching The action of these drugs is temporary and in our experience they do not alter the course of the disorder

Sensitization also may follow the local application of ointments either ophthalmic ointments or ointments for dermatoses This type of sensitization is more frequent than that following the parenteral use of penicillin

Contact dermatitis occurs in nurses and physicians who handle or prepare penicillin solutions It is desirable therefore for all persons who handle penicillin frequently to wear rubber gloves while preparing solutions and to wash all penicillin from the gloves before removing them

Sensitization also may follow the use of aerosol solutions or the use of troches for local infections of the mouth It has caused sensitization following its use in tooth paste Black tongue may follow the use of troches locally

Once a patient has become sensitized he will react to a second injection of penicillin for a long period of time i e a year or longer It is well therefore to proceed with great care if it becomes necessary to use penicillin a second time It has been possible to build up a tolerance to penicillin once a patient has become sensitized by giving small doses such as 1 000 units at intervals of a day or more On the whole however one must proceed cautiously

Sensitization following the injection of peanut oil and wax has been reported somewhat more often than following aqueous penicillin so that this must be taken into account when the preparation is used In general it has not occurred in more than 5 or 7 per cent of patients

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CHAPTER XXX-C

STREPTOMYCIN IN THE TREATMENT OF INFECTIONS

By CHESTER S. KEEFER, M.D.

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Historical Note

Streptomycin was described first by Schatz, Bugie and Waksman The active antibiotic substances that were originally defined as streptomycin are derived from the growth of *Sterptomyces griseus* This is one of the higher bacteria that is found in heavily manured soil although the original strain was isolated from the throat of a chicken Streptomycin is active against both gram positive and gram negative organisms as well as the tubercle bacillus The toxicity of streptomycin for man and animals is low, and it is active for a number of infections in man

Chemistry and Preparation of Solutions

Recent studies have demonstrated the fact that streptomycin as it was defined originally is not a single chemical entity but a mixture of at least two chemically related substances The major constituent sometimes known as streptomycin A is now known to be an o glycoside of the disaccharide streptobiosamine with streptidine The second constituent sometimes known as streptomycin B is o-mannosido-N methyl l glucosaminido streptosido-streptidine

In addition to these two substances the organism produces at least two and possibly three or more antibiotics One is produced by the mycelium and has remained unnamed Another designated as actidione, is found in the culture filtrate and is active only against fungi

Waksman recently has suggested the following nomenclature which may be adopted

Streptomycin complex a term applied to all crude or partially purified preparations containing various forms of streptomycin and inactive impurities in unknown proportions

Streptomycin the compound formerly known as streptomycin A, or N Methyl L glucosaminido streptosido streptidine

Mannosidostreptomycin the compound known as streptomycin B

Streptomycin residue substances remaining after the removal of purified streptomycin from impure streptomycin and which may have antibiotic properties or act as enhancement factors

Streptomycin like substances any preparations produced by the organism which show an antibiotic spectrum and other biological and chemical properties similar to those of streptomycin One such substance has been designated streptomycin II by Johnstone and Waksman

Streptomycin complex is an organic base which readily combines with acid radicles such as the hydrochloride the sulfate or with calcium chloride to form the double salt calcium chloride streptomycin complex All of these salts are available and while the complex is a mixture of streptomycin and mannosidostreptomycin both substances have an antibiotic spectrum The latter differs quantitatively from the former Only time and experiment will determine whether pure compounds are capable of producing more favorable clinical results than the complex and also whether one product is more toxic than the other

Dihydrostreptomycin trihydrochloride —This product is a derivative of streptomycin by catalytic hydrogenation It has been used in place of streptomycin because it produces less neurotoxicity The available

evidence suggests that dihydrostreptomycin is as effective as streptomycin gram for gram in the treatment of tuberculosis and all other infections that are susceptible to the action of streptomycin Also hypersensitivity reactions appear to be less frequent with the dihydrostreptomycin then with streptomycin, and many patients, who are intolerant to streptomycin, have been able to continue therapy with dihydrostreptomycin *In short, dihydrostreptomycin can be used in place of streptomycin, and this is advised with the same dosage schedules as given for streptomycin*

All of the salts of streptomycin complex are biologically active These salts are extremely soluble in isotonic solutions of sodium chloride or in sterile, pyrogen-free, distilled water In view of the fact that sodium chloride may reduce the activity of streptomycin in vitro, it is perhaps better to use solutions in sterile distilled water for clinical administration Solutions may be stored at room temperature under aseptic conditions for one week without significant loss of potency Solutions should not be autoclaved

The salts of streptomycin are dispensed as a dry, sterile powder in airtight rubber capped vials each containing the equivalent of 1 gm or 2 gm (1 000 000 or 2,000 000 units) of streptomycin base Concentrations of 200 to 1,000 mgm per cubic centimeter may be prepared for intramuscular injection and 25 to 50 mgm may be dissolved in 5 to 15 cubic centimeters of normal physiological saline solution for intrathecal injection The solution should be clear and free of undissolved particles and the volume injected into the muscle should be kept as small as possible The site of injection should be changed with each injection the upper quadrants of the buttocks and the anterior thigh muscles are the areas most suitable for injection

Streptomycin Standards

All batches of streptomycin are certified by the Food and Drug Administration before they are released by the manufacturers for sale These certified products have been studied by the manufacturers in an elaborate manner before they are tested by the Food and Drug Administration The rules and regulations for certification have been published in the Federal Register in April 1947 and they are amended from time to time meet new conditions All information concerning the stability of the product and other essential features are contained on the

label and package inserts These should be read carefully by the physician who uses the product

Routes of Administration

There are three common routes of administration of streptomycin or dihydrostreptomycin intramuscular subcutaneous and topical including intrathecal intraperitoneal and intrapleural Solutions may be dropped into the conjunctival sacs into the nasal passages or into the external auditory canal The drug has been given by means of gauze soaks to cutaneous areas and by inhalation and it has been introduced also into the urinary bladder and kidney pelves

The oral route is employed when a local effect in the intestinal tract is desired but this route is of no value in the treatment of systemic infections for the reason that so little streptomycin is absorbed from the gastrointestinal tract

For all systemic infections the intramuscular route is the one of choice Streptomycin may be given subcutaneously but it is more likely to cause pain and local irritation by this route than by the intramuscular one In the treatment of meningitis both intramuscular and intrathecal injections are necessary for optimum results In empyema intrapleural injections are desirable in peritonitis intramuscular and in some cases intraperitoneal injections are required There is no advantage in giving streptomycin intravenously, since it is readily absorbed from the muscles

Intramuscular Injection—When the intramuscular method is used the maximum serum or plasma concentrations of streptomycin are obtained within 1 to 3 hours after single injections and there is a gradual decrease in the concentration over a period of 10 to 1 hours There is a correlation between the plasma concentration and the amount of streptomycin administered Additive effects are obtained by repeating the injections at 4 hour intervals

In general it can be said that the total daily dose may be divided into two or four equal amounts and given every 6 to 12 hours throughout the day

Following intramuscular injection streptomycin enters the blood and passes freely into the pleural fluid the peritoneum the ocular fluid and the bile It diffuses across the placenta into the fetal circulation and amniotic fluid and it has been found in the umbilical cord blood

and amniotic fluid within 10 minutes after intravenous injection into the maternal circulation Very little streptomycin diffuses into the cerebrospinal fluid There is also evidence that it diffuses into the pus of soft tissue abscesses, and it can be found in the kidney and other tissues of the body in varying concentration following intramuscular injection While the drug diffuses into the pleural and peritoneal fluid the concentration there usually is lower than that of the blood The same is true for bile ocular fluid, the fetal blood and amniotic fluid

In brief, then streptomycin diffuses from the blood into the body fluids and tissues but the concentration in the various tissues is usually much lower than that in the circulating blood

There is no good evidence that streptomycin is destroyed in the body *Most of it is excreted by the kidneys into the urine, small amounts* are excreted into the bile and appear in the feces At least 60 to 80 per cent of the streptomycin that is injected intramuscularly may be recovered in the urine within a 24 hour period

Subcutaneous Injection—It has been stated already that intermittent subcutaneous injection may be used in place of intramuscular injection It is much more likely however, to cause pain and local irritation, and this route has no advantages over the intramuscular one Maximum plasma concentrations are observed within 2 to 3 hours after subcutaneous injection

Intrathecal Injection—Following intrathecal injection streptomycin leaves the subarachnoid space slowly, so that relatively high concentrations can be detected in the cerebrospinal fluid throughout a 24 hour period following a single injection of as little as 20 mgm The average amount injected intrathecally should be 25 to 50 mgm daily in some cases it may be necessary to use as much as 100 mgm, *but this amount should not be exceeded and should be used only when an unfavorable response has been obtained with smaller dosage in patients with bacterial meningitis*

Oral Administration—So little streptomycin is absorbed from the gastrointestinal tract that it should not be given by this route unless one is anxious to reduce the total number of bacteria in the stools This method of therapy has been used as a prophylactic measure in preparing patients for surgical operations on the large bowel It has been employed also without much success in the treatment of local and systemic infections beginning in the intestine such as typhoid fever and Salmon

ella infections Two to 3 gm a day by mouth may be necessary to reduce the number of bacteria in the stools

Inhalation —Streptomycin can be inhaled in aerosolized solutions for the treatment of bronchopulmonary infections due to gram negative bacilli or it may be combined with penicillin when a mixed infection is present Concentrations of 50 mgm per cubic centimeter may be inhaled after the drug has been nebulized so that a total amount of 500 mgm in a 24 hour period is administered in this way Only small amounts of streptomycin are absorbed from the lungs so that very little is detected in the blood plasma and small amounts may be recovered from the urine

Topical Administration (Wound Infections, Ocular Infections External Otitis) —Solutions containing 25 to 50 mgm per cubic centimeter may be used locally in the conjunctival sac for infections of the conjunctiva or cornea The same solutions may be used in the treatment of external otitis due to gram negative organisms

Intrapleural or Intraperitoneal Injection —One half (0 5) or 1 gram of streptomycin may be dissolved in o to 50 c c of sterile physiological salt solution and injected directly into the pleural or peritoneal cavities These injections may be repeated every 1 or 4 hours *Irrigations are ineffective*

Bacterial Resistance and Sensitivity

It is now generally recognized that there is a great variation in the sensitivity of various organisms to the action of streptomycin It is desirable to know about the sensitivity of the organism that is causing infection in order that enough streptomycin may be given so that the concentration in the blood and tissues will be sufficient to inhibit the growth of the infecting organism In Table I which is taken from a paper by Murray Paine and Finland there are listed the reported range and the sensitivity that is most frequently encountered in a wide variety of micro organisms It is plain from this table that there is a wide variation in the sensitivity of different organisms to streptomycin and it is striking that there is also considerable variation from one strain to another within the same species

Inasmuch as it has been demonstrated that in the presence of blood or serum the tolerance of micro-organisms to streptomycin may be increased four to eight times it is desirable to maintain a concentration in the blood four to eight times that necessary to inhibit completely the growth of organisms in vitro

One of the striking features of the use of streptomycin in the treatment of infections is the rapidity with which many bacteria acquire resistance to it. That is to say, following treatment with the drug organisms appear in local foci of infection that cannot be killed by concentrations that can be obtained by the clinical use of the drug. The rapid development of resistance should encourage one to adopt the maximum dosage that is indicated in the very beginning of treatment. While it has not been demonstrated that all resistant bacteria are virulent and cause continuing infection, it is true that the appearance of resistant organisms may account for a number of streptomycin failures.

TABLE I

SENSITIVITY OF VARIOUS ORGANISMS TO STREPTOMYCIN

ORGANISM	*REPORTED SENSITIVITY*	
	Range	Most Frequent
Actinomyces bovis	4	–
Aerobacter aerogenes	0.5–128	6–5
Bacillus anthracis	0.5	
Bacillus cereus	0.8–2	
Bacillus megatherium	0.25–8	–
Bacillus subtilis	0.1–128	1–8
Brucella abortus	0.5–4	
Brucella melitensis	0.5–2	
Brucella suis	0.5–3	
Clostridium perfringens (Welch bacillus)	>104	
Clostridium septicum (Vibrion septique)	>105	
Clostridium sordelli	>105	
Clostridium tetani	>104	
Coccidioides immitis	>300	
Corynebacterium diphtheriae	0.4–4	
Diplococcus pneumoniae (pneumococcus)	4–50	
Diphtheroids	1–>128	
Eberthella typhosa	1–120	1–16
Erysipelothrix muriseptica	2.5	
Escherichia coli (various strains)	0.3–128	<8
Haemophilus ducreyi (chancroid)	1–5	
Haemophilus hemolyticus	0.8–3	

Minimum inhibiting concentration of streptomycin in micrograms per cubic centimeter of culture

ORGANISM	*REPORTED SENSITIVITY* Range	Most Frequent
Haemophilus influenzae (Pfeiffer's bacillus)	1–50	1–5
Haemophilus parainfluenzae	· 3	
Haemophilus pertussis	1–15	1–3
Histoplasma capsulatum	>2500	
Klebsiella ozaenae	0 –1 5	
Klebsiella pneumoniae (Friedlander's bacillus)	0 .–128	0 6–8
Listerella monocytogenes	2 5	
Malleomyces mallei (glanders)	10–>10	
Mycobacterium tuberculosis (avian)	10–50	
Mycobacterium tuberculosis (human and bovine)	0 1–1	
Neisseria catarrhalis	1–4	
Neisseria gonorrhoeae (gonococcus)	5–40	10–15
Neisseria intracellularis (meningococcus)	1–40	
Nocardia	4–1 5	
Pasteurella pestis (plague)	0 5–1 5	
Pasteurella tularensis	0 1–0 3	
Paracolon bacillus	–1 8	–16
Proteus morgani	1–1 8	8–50
Proteus vulgaris	0 4–128	4– 5
Pseudomonas aeruginosa (Bacillus pyocyaneus)	– 00	8–50
Salmonella (various species)	4–1 0	4–32
Sarcina lutea	0 .5	
Serratia marcescens (Bacillus prodigiosus)	1–64	
Shigella (various species)	0 2–8	3–7
Staphylococcus albus	1–256	1–4
Staphylococcus aureus	0 5–>128	1–8
Streptococcus faecalis	1 5–60	
Streptococcus Haemolyticus	1–>1 8	2–3
Streptococcus nonhemolytic	1–>1 8	1–32
Streptococcus viridans	0 1–>1 8	1–3.
Streptomyces (various species)	0 4–1 5	
Veillonella gazogenes	10	
Vibrio comma (cholera)	5–>500	

Minimum inhibiting concentration of streptomycin in micrograms per cubic centimeter of culture

One of the striking features of the use of streptomycin in the treatment of infections is the rapidity with which many bacteria acquire resistance to it. That is to say, following treatment with the drug organisms appear in local foci of infection that cannot be killed by concentrations that can be obtained by the clinical use of the drug. The rapid development of resistance should encourage one to adopt the maximum dosage that is indicated in the very beginning of treatment. While it has not been demonstrated that all resistant bacteria are virulent and cause continuing infection, it is true that the appearance of resistant organisms may account for a number of streptomycin failures.

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Aerobacter aerogenes	0 5–128	6–.5
Bacillus anthracis	0 5	
Bacillus cereus	0 8–2	
Bacillus megatherium	0 25–8	–
Bacillus subtilis	0 1–128	1–8
Brucella abortus	0 5–4	
Brucella melitensis	0 5–[illegible]	
Brucella suis	0 5–3	
Clostridium perfringens (Welch bacillus)	>104	
Clostridium septicum (Vibrion septique)	>105	
Clostridium sordelli	>105	
Clostridium tetani	>104	
Coccidioides immitis	>300	
Corynebacterium diphtheriae	0 4–4	
Diplococcus pneumoniae (pneumococcus)	4–50	
Diphtheroids	1–>1.8	
Eberthella typhosa	1–1.0	1–16
Erysipelothrix muriseptica	2 5	
Escherichia coli (various strains)	0 3–1.8	<8
Haemophilus ducreyi (chancroid)	1–5	
Haemophilus hemolyticus	0 8–3	

Minimum inhibiting concentration of streptomycin in micrograms per cubic centimeter of culture

7 to 9 days after treatment is discontinued Skin eruptions may or may not be accompanied by fever When fever is present it usually persists for 1 to 5 days Rarely fever occurs without skin eruption

When patients have developed a skin eruption following streptomycin they frequently react to a single injection at a later date with the reappearance of a rash or fever It is well therefore to ask every patient who is about to receive streptomycin whether or not he has received it previously The longer is the interval of time between the initial hypersensitive reaction and the reinjection the less likely is one to observe the recurrence of fever and a skin rash following a reinjection

In general it is advisable to stop streptomycin if the skin eruption appears Certainly the dosage should be reduced and if treatment is continued it should be carried forward with considerable caution Relief from the burning and itching that may be associated with the skin eruption may be obtained by the use of benadryl in 50 to 100 mgm doses three or four times a day

Eosinophilia

This sign of hypersensitivity to streptomycin was first reported by McDermott The eosinophiles may be 5 per cent or higher and the eosinophilia may continue throughout treatment It may be an accompanying feature of the skin eruption but it may also appear without any eruption whatsoever So far there has been no correlation between the eosinophilia and the onset of neurological symptoms although the two occasionally are present in the same patient

Neurological Disturbances

The three neurological abnormalities that have been described are disturbances in equilibrium (vertigo without the rotary component) deafness and tinnitus Occasionally patients have complained of paresthesias in the region of the second and third branch of the 5th cranial nerve Also there has been some transitory blurring of vision in occasional patients These complaints usually are temporary and disappear within several days after the drug has been discontinued

Vertigo — In virtually all patients receiving as much as 3 gm of streptomycin a day vertigo has been observed between the 17th and

Streptomycin Dependence

One of the most interesting phenomena that has been described in connection with the change in bacteria following their exposure to streptomycin is the appearance of strains of bacteria that are dependent upon streptomycin for their growth This feature was described first by Miller and Bohnhoff for strains of meningococci and since then they have found many other species of bacteria that show strains that are dependent upon streptomycin for their growth These observations have been confirmed and extended by Finland and his associates

So far it has not been demonstrated that streptomycin dependent strains are responsible for a continuing infection while streptomycin is being administered It is a phenomenon that should be looked for in man since it might be important in understanding the failure of streptomycin to control an infection while it is being administered

Side Reactions

There are two important side reactions to streptomycin, neurological disturbances characterized by tinnitus, vertigo or deafness and hypersensitive reactions characterized by fever skin eruptions and eosinophilia Pain in the muscles at the site of local injection is complained of by a number of patients regardless of the preparation used It is more frequent when large amounts—0 5 to 1 gm —are given at a single injection in relatively large volumes of fluid that is, more than 2 cubic centimeters It is desirable to change the site of injection frequently and to use as small a volume of streptomycin as possible One cubic centimeter of 1 per cent solution of procaine hydrochloride may be given with each injection to minimize pain

Histamine-like reactions were described when streptomycin was first introduced These are no longer encountered because the method of preparation has eliminated histamine from the product

Sensitization reactions are characterized by fever and skin eruptions in about 5 per cent of patients The eruptions may be erythematous urticarial maculopapular or even hemorrhagic The rashes appear most often between the 3rd and 10th day of treatment, but they may be observed as early as the 2nd day Sometimes they do not occur until after treatment has been stopped Their duration is extremely variable They may be transitory and disappear within 1 to 3 days in spite of continuation of treatment whereas in other cases they may last for

can be controlled Infections with bacteremia due to a variety of organisms have been treated These include *Escherichia coli Proteus vulgaris, Pseudomonas aeruginosa, Aerobacter aerogenes, Klebsiella pneumoniae, Hemophilus influenzae* and Salmonella In all these cases the fatality rate has been reduced and in patients who have recovered the streptomycin was important in controlling the local infection It is generally recognized that the prognosis in such cases is determined in some measure by the nature and severity of the local lesions from which the invasion of the blood stream occurs In some cases also it is known that the bacteremia is a transitory one and often follows trauma to an infected area The age of the patient the site and extent of the initial lesion the species of infecting organism the presence of complicating and debilitating diseases and the duration of infection must be taken into account in assessing the results of treatment All patients with bacteremia should receive 1 to 3 gm of streptomycin daily for a period of 7 to 10 days

The overall results of treatment with streptomycin in 309 cases of bacteremia are shown in Table II

TABLE II

STREPTOMYCIN TREATED

OVERALL RESULTS IN PATIENTS WITH BACTEREMIA

Organism	No of Cases	Permanent Improvement Per Cent	Temporary Improvement Per Cent	No Effect Per Cent
Aer aerogenes	23	61	13	6
E coli	132	63	12	25
Kleb pneumoniae	19	63	16	21
H influenzae	80	8	5	15
P vulgaris	16	75	6	19
Ps aeruginosa	19	47	6	47
Unidentified gram negative bacilli	9	56	13	31
Salmonella	11	73	9	18
	309			

STREPTOMYCIN IN TULAREMIA

All clinical forms of tularemia respond to streptomycin in a remarkable manner In fact, it can be said that streptomycin is the most

25th days It is much less frequent when smaller doses are used that is 0 5 to 1 gm a day for 5 to 14 days When the disturbance in equilibrium occurs early, it is most often complained of during the first 5 days It may be severe or mild, and it may last from 1 day in the very mild cases to 30 or 60 days in the severe ones, in some cases it has persisted for as long as 6 to 9 months In the patients described by McDermott all were completely free of symptoms at the end of 4 months In 1 out of 10 patients with disturbances of equilibrium the symptom is severe It may be associated with nausea and vomiting In half the patients it is moderately severe, and in about a third it is negligible Disturbance in equilibrium is most noticeable after sudden movement such as turning over or sitting up in bed but at the height of the reaction patients are uncomfortable even when lying flat The acute symptoms persist for 7 to 10 days and then gradually subside to such a degree that only an unusual stimulus such as sudden shaking of the head produces transitory symptoms Rarely patients continue to feel unsteady at the beginning of walking or after rising from a chair, and this condition may persist for a number of months

Deafness — This reaction is extremely uncommon, but it has been reported under several different circumstances, first, when very large daily doses of streptomycin — 6 to 9 gm — are used, secondly in patients with marked renal insufficiency thirdly in patients who have meningitis and receive the drug intrathecally The deafness varies tremendously both in degree and in duration In some cases it is transitory and is often associated with tinnitus This is particularly true of patients who have become deaf after receiving relatively small amounts of streptomycin within the first week of treatment In others the deafness is permanent and it may be complete, or the hearing may be reduced by approximately 50 per cent

Tinnitus — This is a frequent complaint and may be associated either with deafness or with disturbances in equilibrium It has occurred in approximately 5 per cent of the cases reported to the Committee on Chemotherapy It usually disappears following the discontinuance of streptomycin

Streptomycin in Bacteremia

Bacteremias due to a wide variety of gram negative bacilli with or without localizing signs of infection can be cleared by streptomycin in many cases and the local infection responsible for the blood invasion

centration of 20 mgm per cubic centimeter of streptomycin Strains of *Strept faecalis* and *Ps aeruginosa* are often extremely resistant in the very beginning and require concentrations of at least 100 mgm or more to inhibit their growth When streptomycin is given to patients with acute or chronic pyelonephritis constitutional symptoms and signs of infection frequently disappear promptly Clinical improvement occurs in 50 to 60 per cent of the patients within a 7- hour period Symptoms referable to the urinary tract respond more irregularly

It has been our experience that when the urinary output is restricted to 000 cubic centimeters a day and the daily dose of streptomycin is 1 gm the concentration of streptomycin in the urine averages about 100 mgm per cubic centimeter This usually is adequate for the treatment of most urinary tract infections provided other factors are favorable for sterilizing the urine When resistant organisms such as *Ps aeruginosa* and *Strept faecalis* are present a higher urinary concentration of streptomycin is desirable and a daily dose of - gm should be given When single organisms are present sterilization of the urine occurs in about 40 per cent of the cases Bacteriuria is diminished at least temporarily in practically all patients Infections due to a single organism generally respond much more favorably than do those in which a mixed bacterial flora is present Any patient who fails to respond within 4 to 7 hours should be suspected of having a resistant organism or some underlying anatomical lesion interfering with the free flow of urine a foreign body or an undrained abscess It should be remembered that bacteria exposed to streptomycin may if the strains have become resistant to it often respond to other chemotherapeutic agents

In summary then in the treatment of urinary tract infections it is desirable to study the organisms that are causing infection in order to determine their resistance and also to examine the patient for an explanation of the underlying cause of infection When obstructions are present plans should be made to establish a free flow of urine or for the removal of stones The urinary output should not exceed 2 000 cubic centimeters a day Streptomycin should be given intramuscularly in 1 0 gm doses for a period of 5 to 7 days and the urine should be kept alkaline during this time Usually it is unnecessary to continue treatment longer than 7 to 10 days unless bacteremia and an invasive infection are present Under these circumstances it may be necessary to continue treatment for as long as - to 3 weeks before the infection is under complete control

important chemotherapeutic agent available today for the treatment of this disease The results from it have been striking This is one of the infections in which relatively small amounts of streptomycin have been used successfully Five tenths to 1 gm a day in divided doses every 6 hours for 6 days usually is adequate to control either the ulceroglandular or the pneumonic form of tularemia Intermittent intramuscular injections given over a period of 6 days are followed usually by a period of rapid decrease in the temperature within 48 to 72 hours and by improvement in the constitutional symptoms There is a more gradual decrease in the size of the lymph nodes often without suppuration, and a slow regression of the x ray and physical signs of pneumonitis when they are present The clinical results of treatment have been extremely impressive in the typhoidal form of the disease as well as in the ulceroglandular and pulmonary forms

All patients suspected of having tularemia should be treated promptly, for the reason that the results are so striking and impressive The optimum results are obtained with 1 0 gram a day for a minimum period of 6 days

Streptomycin in Urinary Tract Infections

Acute and chronic urinary tract infections due to susceptible micro-organisms usually of the gram negative group have responded in a remarkable way in at least 40 to 60 per cent of the cases following the use of streptomycin Following parenteral injection, 60 to 80 per cent of the amount injected is recovered in the urine within 24 to 48 hours Streptomycin usually appears in high concentration depending on the renal function the volume of the urine and the dose administered It is much more active when the urine is alkaline so that it is desirable to use alkalis along with streptomycin to render the urine alkaline if it is not already so In susceptible cases the urine usually is sterilized within a period of 72 hours Failure to sterilize the urine within this period of time is due generally to resistance of the infecting organism the presence of an obstruction in the urinary tract an undiscovered abscess or a foreign body It is practically impossible to sterilize the urine when there is an indwelling catheter, or when stones are present

The commonest micro-organisms causing urinary tract infections are *Escherichia coli, Aerobacter aerogenes, Proteus vulgaris Pseudomonas aeruginosa* and *Streptococcus faecalis* At least 75 per cent of the strains of *Esch, coli, P vulgaris* and *A, aerogenes* are sensitive to a con

responsible for recoveries and it should be given in all cases One gram a day intramuscularly in divided doses and 5 to 50 mgm a day intrathecally with treatment continued for 6 to 10 days depending on the clinical response is the regime to be followed

The results that have been obtained are summed up in Table III

TABLE III

Type of Infecting Organism	No of Cases	Recovered	Died
E coli	1[illegible]	9	3
Ps aeruginosa	11	6	5
Aerobacter aerogenes	1	0	1
Proteus vulgaris	2	2	0
Str faecalis	3	1	2
Kleb pneumoniae	4	2	2
Gram negative bacilli unidentified	9	8	1

Some facts concerning these cases are of interest

E Coli Meningitis —This is a disorder primarily of infancy and the newly born The meningitis commonly is accompanied by bacteremia In some patients there is a story of daily spinal punctures for drainage of cerebrospinal fluid following birth trauma or for subarachnoid hemorrhage and open decompression for the relief of hydrocephalus The onset is sudden with high fever and signs of meningeal irritation The effective dosage schedule has been 1 gram a day intramuscularly and o to 50 mgm a day intrathecally This treatment should be continued for at least 1 to 2 weeks in order to obtain the optimum results and reduce the relapse rate to a minimum

Ps aeruginosa —This form of bacterial meningitis commonly follows lumbar puncture for diagnosis or for spinal anesthesia There are many streptomycin resistant strains so that the treatment may be unsatisfactory Only about 55 per cent of patients have recovered and relapses are common

It is necessary therefore to give - grams of streptomycin a day intramuscularly and 50 mgm of streptomycin intrathecally daily for a minimum period of 14 days

The other bacterial forms of meningitis tested in Table III required the same type of treatment as *H influenzae*, *E coli* and *Ps aeruginosa* infection

Streptomycin in *H Influenzae* Meningitis

This is a common form of meningitis in infants and children under the age of five years While the meningitis may follow an infection of the upper respiratory passages, it is common for this infection to be overlooked so that no primary focus is uncovered

Bacteremia occurs in at least 35 per cent of cases, and one may also find pneumonia or otitis media associated with the meningitis In 207 patients with *H influenzae* meningitis treated with streptomycin, the fatality rate was 20 per cent The following points are important in treatment Systemic and intrathecal injections should be given as soon as the diagnosis is established A delay in the recognition of the disease and its treatment reduces the patient's chances of recovery The minimum daily dose should be 1 gram of streptomycin intramuscularly for at least 8 to 10 days and 5 mgm of streptomycin intrathecally for 4 to 7 days

One of the limiting factors of streptomycin treatment has been the emergence of resistant bacteria during exposure to streptomycin A low concentration of sugar in the cerebrospinal fluid is an index of *intra* meningeal bacterial activity so that a very low concentration, i e below 20 mgm, always suggests a severe infection and decreases the chances for recovery Also the prognosis is poor in patients under the age of 6 months

Finally, the results are more favorable when the sulfonamides are combined with streptomycin in treatment If streptomycin resistant organisms emerge during treatment, then type specific antiserum should be employed

Streptomycin in Meningitis Due to Miscellaneous Gram Negative Bacilli

Occasional cases of meningitis are caused by *Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Proteus vulgaris, Alcaligenes faecalis, Proteus morganii, Salmonella cholerae suis* and *Aerobacter aerogenes* The fatality rate in these cases tends to be high although the use of streptomycin both intramuscularly and intrathecally in adequate doses early in the course of the disease, has been followed by favorable results Infections of the central nervous system by these organisms respond poorly to the sulfonamides and are not helped by penicillin When patients are treated early, it is clear that streptomycin has been

responsible for recoveries and it should be given in all cases One gram a day intramuscularly in divided doses and 25 to 50 mgm a day intrathecally with treatment continued for 6 to 10 days depending on the clinical response is the regime to be followed

The results that have been obtained are summed up in Table III

TABLE III

Type of Infecting Organism	No of Cases	Recovered	Died
E coli	12	9	3
Ps aeruginosa	11	6	5
Aerobacter aerogenes	1	0	1
Proteus vulgaris	[illegible]	2	0
Str faecalis	3	1	[illegible]
Kleb pneumoniae	4	2	2
Gram negative bacilli unidentified	9	8	1

Some facts concerning these cases are of interest

E Coli Meningitis — This is a disorder primarily of infancy and the newly born The meningitis commonly is accompanied by bacteremia In some patients there is a story of daily spinal punctures for drainage of cerebrospinal fluid following birth trauma or for subarachnoid hemorrhage and open decompression for the relief of hydrocephalus The onset is sudden with high fever and signs of meningeal irritation The effective dosage schedule has been 1 gram a day intramuscularly and 20 to 50 mgm a day intrathecally This treatment should be continued for at least 1 to weeks in order to obtain the optimum results and reduce the relapse rate to a minimum

Ps aeruginosa —This form of bacterial meningitis commonly follows lumbar puncture for diagnosis or for spinal anesthesia There are many streptomycin resistant strains so that the treatment may be unsatisfactory Only about 55 per cent of patients have recovered and relapses are common

It is necessary therefore to give grams of streptomycin a day intramuscularly and 50 mgm of streptomycin intrathecally daily for a minimum period of 14 days

The other bacterial forms of meningitis tested in Table III required the same type of treatment as *H influenzae, E coli* and *Ps aeruginosa* infection

Streptomycin in Respiratory Infections

Infections of Epiglottis and Laryngotracheobronchitis—These infections often are associated with an invasion of the tissues by *H influenzae* When this proves to be the case, then streptomycin is indicated The results in a small number of cases reported to us were highly satisfactory Streptomycin in doses of 1 gram a day has proved to be adequate

Lung Abscess—In cases of chronic abscess of the lung, due to a mixed infection in which gram negative organisms predominated, two thirds of them have improved under treatment The amount of streptomycin has varied from 0 5 to 3 grams a day, and it has been continued from one week to one month, depending upon the course of the disease

Pertussis—There is very little information available concerning the value of streptomycin in pertussis It is admitted that this is a disorder of variable course so that the effect of any particular form of treatment is difficult to assess unless large numbers of cases are treated under careful supervision When pneumonia is present, streptomycin has influenced the course of this complication favorably One-half to 1 gram has been given daily for 6 to 14 days Streptomycin deserves wider use in the treatment of this disease

Streptomycin in Pulmonary Infections

The two commonest organisms causing acute infection of the lungs that are susceptible to streptomycin are *Hemophilus influenzae* and *Klebsiella pneumoniae* These infections may be either acute or chronic and either primary or secondary In the chronic infections there is always some underlying anatomical lesion, such as bronchiectasis that contributes to the infection In the acute infections with pneumonitis due to *Kleb pneumoniae* and *H influenzae* the results of streptomycin treatment have been impressive In the chronic infections, on the other hand, they have been transitory *H influenzae* infection of the lungs is seen most often in infants and young children Here a diffuse capillary bronchitis or bronchopneumonia is frequent, and in about half the patients it is accompanied by bacteremia Streptomycin has been highly successful in the treatment of these acute infections in infancy and childhood

In *Kleb pneumoniae* infections the acute infection is often controlled

so that the process does not go on to abscess formation and pulmonary fibrosis In view of the serious character of pneumonia caused by *Kleb pneumoniae*, its associated high fatality rate and its tendency to produce multiple pulmonary cavities prompt institution of large doses of streptomycin preferably 0 5 gm every 6 hours in adults is indicated

It is a common experience to observe a change in the bacteriological flora of the sputum of patients with pulmonary infections who have been treated with antibiotic agents Following penicillin it is not infrequent for the gram positive organisms to disappear or at least to become less numerous and for gram negative organisms to appear in large numbers In many cases it is extremely difficult to decide what role is being played by these organisms in continuing infections In some cases they seem to be important for the reason that following streptomycin treatment the constitutional symptoms and signs of infection may disappear as the organisms disappear from the sputum In some of the mixed infections it may be necessary to give both penicillin and streptomycin

Chronic Pulmonary Infections

Chronic bronchiectasis lung abscess and empyema caused by gram negative organisms may be helped by streptomycin given either by the aerosol method or systemically In many cases these infections are a mixed variety so that it is necessary to use both penicillin and streptomycin Penicillin eliminates only the penicillin senitive organisms and in some patients the infection persists owing to the presence of gram-negative bacilli which are penicillin insensitive It is in such cases that the response to streptomycin has been encouraging The number of organisms is decreased following inhalations of streptomycin and the volume of the sputum may diminish At least 0 5 gm of streptomycin in 0 cubic centimeters of normal physiological salt solution should be given daily It should be stressed that streptomycin is only palliative in these cases but it offers great relief of symptoms and in some cases it arrests the progress of the disease

Streptomycin in Tuberculosis

Soon after it had been demonstrated that streptomycin inhibits the growth of the tubercle bacillus in vitro experimental studies were car

ried out in guinea pigs with tuberculous infection by Feldman and Hinshaw at the Mayo Clinic They demonstrated quite conclusively that in at least 70 per cent of animals infected with tubercle bacilli streptomycin was responsible for eliminating the organisms from the body

The most extensive studies on the effect of the drug in tuberculosis have been carried out by the Veterans Administration under the direction of Barnwell and Waller Other important studies have been carried out by the Army and the Navy, by Hinshaw and Feldman and their associates at the Mayo Clinic and by McDermott and his associates at the New York Hospitals

It is proper to say at once that streptomycin is the only effective chemotherapeutic agent that can be used in man for the treatment of tuberculosis In a few cases it has been combined with promine In some cases extraordinary results have been observed

Acute Miliary Tuberculosis with or without Meningitis—Patients with miliary tuberculosis without meningitis have recovered from their acute disseminated process in about two-thirds of the cases These results have been obtained when patients have received 2.0 gm of streptomycin daily for 120 days The follow-up period has averaged 4 months to a year When death occurs in this group it commonly occurs within 6 weeks of the initiation of treatment In most of the fatal cases there has been no evidence of healing of the lesion at postmortem In a few, however, evidence of healing is plain and consists of small fibrotic hard tubercles many of them have lost their characteristic histological appearance Patients who relapse while under treatment often show an infection due to a resistant organism In about half of the patients with miliary tuberculosis, who recover from signs of disseminated lesions meningitis appears within 4 weeks to 4 months after treatment has been started In patients with both miliary tuberculosis and meningitis only about 10 per cent have recovered following treatment

In patients with meningitis without miliary tuberculosis about one third of the patients recover from the signs of acute infection, but only about 25 per cent are relieved of all evidence of central nervous system tuberculosis Even in these cases the protein content of the cerebrospinal fluid continues to be elevated in spite of the normal cell count

It has been suggested by the Veterans Administration group that the dosage schedule for miliary tuberculosis should be 2.0 gm daily in 5 doses and the treatment should be continued from 90 to 180 days depending upon the response of the patient When meningitis is present

the parenteral treatment should be combined with intrathecal injections of 0.05 gm per day for the first week then two or three times a week or less often as improvement takes place In view of the favorable responses in children with miliary tuberculosis following the use of promin it has been suggested further than 4.0 gm of promin a day be given intravenously for 2 weeks followed by a week of rest When promin is used the blood must be watched carefully since a hemolytic anemia may occur

The results of treatment of these serious cases of tuberculosis may be summed up as follows —

1) Patients with acute miliary tuberculosis recover from the signs of infection more often when there are no signs of tuberculous meningitis present at the onset of treatment
2) The optimum results have been obtained with 2 gm of streptomycin intramuscularly for 120 days in divided doses 5 times a day
3) Fifty milligrams of streptomycin should be given intrathecally during the first week then two or three times a week as improvement occurs

Failures are due most often to the following —

1) The presence of meningitis
2) The development of meningitis during or following the discontinuance of treatment
3) The development of bacterial resistance

Progressive Pulmonary Tuberculosis —The effect of streptomycin in some patients with progressive pulmonary tuberculosis has been striking indeed It is most impressive in the patients with acute exudative lesions and in the areas of the lung where necrosis is minimal The optimum time dose schedules have not been completely worked out but the immediate results as judged by x ray examinations would appear to be similar whether 1 8 or 2 0 gm are given daily in five divided doses for 60 or 120 days or whether 1 0 gm is given for 60 days either in 5 divided doses or in 2 equal doses Between 75 and 85 per cent of patients will show improvement on these dosage schedules Soon after treatment is started there is often an improvement in the constitutional symptoms and signs Fever is reduced the appetite improves and the patients gain weight Within 1 or 2 months of treatment exudates are being absorbed and there is a gradual regression of the lesions Extensions of the lesions while patients are under treatment are infrequent unless the tubercle bacilli become resistant to streptomycin Between

ried out in guinea pigs with tuberculous infection by Feldman and Hinshaw at the Mayo Clinic They demonstrated quite conclusively that in at least 70 per cent of animals infected with tubercle bacilli streptomycin was responsible for eliminating the organisms from the body

The most extensive studies on the effect of the drug in tuberculosis have been carried out by the Veterans Administration under the direction of Barnwell and Walker Other important studies have been carried out by the Army and the Navy by Hinshaw and Feldman and their associates at the Mayo Clinic and by McDermott and his associates at the New York Hospitals

It is proper to say at once that streptomycin is the only effective chemotherapeutic agent that can be used in man for the treatment of tuberculosis In a few cases it has been combined with promine In some cases extraordinary results have been observed

Acute Miliary Tuberculosis with or without Meningitis—Patients with miliary tuberculosis without meningitis have recovered from their acute disseminated process in about two-thirds of the cases These results have been obtained when patients have received 2 0 gm of streptomycin daily for 120 days The follow-up period has averaged 4 months to a year When death occurs in this group, it commonly occurs within 6 weeks of the initiation of treatment In most of the fatal cases there has been no evidence of healing of the lesion at postmortem In a few however evidence of healing is plain and consists of small, fibrotic "hard" tubercles, many of them have lost their characteristic histological appearance Patients who relapse while under treatment, often show an infection due to a resistant organism In about half of the patients with miliary tuberculosis, who recover from signs of disseminated lesions meningitis appears within 4 weeks to 4 months after treatment has been started In patients with both miliary tuberculosis and meningitis only about 10 per cent have recovered following treatment

In patients with meningitis without miliary tuberculosis about one third of the patients recover from the signs of acute infection, but only about 25 per cent are relieved of all evidence of central nervous system tuberculosis Even in these cases the protein content of the cerebrospinal fluid continues to be elevated in spite of the normal cell count

It has been suggested by the Veterans Administration group that the dosage schedule for miliary tuberculosis should be 2 0 gm daily in 5 doses and the treatment should be continued from 90 to 180 days depending upon the response of the patient When meningitis is present,

the parenteral treatment should be combined with intrathecal injections of 0 05 gm per day for the first week then two or three times a week or less often as improvement takes place In view of the favorable responses in children with miliary tuberculosis following the use of promin it has been suggested further than 4 0 gm of promin a day be given intravenously for . weeks followed by a week of rest When promin is used the blood must be watched carefully since a hemolytic anemia may occur

The results of treatment of these serious cases of tuberculosis may be summed up as follows —

1) Patients with acute miliary tuberculosis recover from the signs of infection more often when there are no signs of tuberculous meningitis present at the onset of treatment
2) The optimum results have been obtained with 2 gm of streptomycin intramuscularly for 1 0 days in divided doses 5 times a day
3) Fifty milligrams of streptomycin should be given intrathecally during the first week then two or three times a week as improvement occurs

Failures are due most often to the following —

1) The presence of meningitis
2) The development of meningitis during or following the discontinuance of treatment
3) The development of bacterial resistance

Progressi e Pulmonary Tuberculosis —The effect of streptomycin in some patients with progressive pulmonary tuberculosis has been striking indeed It is most impressive in the patients with acute exudative lesions and in the areas of the lung where necrosis is minimal The optimum time dose schedules have not been completely worked out but the immediate results as judged by x ray examinations would appear to be similar whether 1 8 or o gm are given daily in five divided doses for 60 or 1 0 days or whether 1 0 gm is given for 60 days either in 5 divided doses or in 2 equal doses Between 75 and 85 per cent of patients will show improvement on these dosage schedules Soon after treatment is started there is often an improvement in the constitutional symptoms and signs Fever is reduced the appetite improves and the patients gain weight Within 1 or 2 months of treatment exudates are being absorbed and there is a gradual regression of the lesions Extensions of the lesions while patients are under treatment are infrequent unless the tubercle bacilli become resistant to streptomycin. Between

15 and 20 per cent of patients have relapses of their infections after treatment is discontinued Only about 50 per cent of patients revert from a positive to negative sputum while under treatment, and with the continuation of treatment for more than 4 to 6 weeks the number of cases, in which the tubercle bacillus becomes resistant to increasing amounts of streptomycin increases greatly For example, it has been shown that only about 5 per cent of strains are resistant to 10 micro grams of streptomycin per cubic centimeter after 28 days of treatment, whereas 76 per cent of organisms are resistant after 120 days In general it can be said that one of the limiting factors in treating patients with tuberculosis is the development of resistant strains of tubercle bacilli These organisms are virulent for guinea pigs Progress of the tuberculous process has been noted in many resistant cases receiving streptomycin In some cases, improvement was noted or continued even though resist ant organisms are obtained on culture In brief however, streptomycin exerts little, if any beneficial effect in cases with resistant organisms and any improvement noted under these circumstances must be attributed to the natural defense mechanism of the disease

Draining Sinuses —Patients with draining sinuses from bone or lymph node tuberculosis improve in a striking manner following streptomycin Sixty per cent of the sinuses heal, and about 25 per cent improve The dose of 1 0 gm a day in two equally divided doses of 0 5 gm each for 120 days is the advantageous dose

Tuberculosis of the Upper and Middle Respiratory Tract —Striking results have been obtained in the treatment of tuberculosis of the upper and middle respiratory tract including the larynx, hypopharynx trachea and larger bronchi Ulcerations have healed in a remarkable manner within 3 to 6 months of treatment and one can observe these healing lesions by direct visual examination The positive effects follow both systemic and local treatment by the aerosol method Systemic treatment appears to be the more effective of the two The recom mended dosage is 1 to 2 gm a day intramuscularly and 0 5 gm in divided doses by inhalation every 2 hours in concentrations of 50 mgm per cubic centimeter

Tuberculosis of the Urinary Tract —Symptomatic improvement has been observed in some patients with tuberculosis of the urinary tract The total number of tubercle bacilli decreases and in a few cases they disappear at least temporarily Pyuria diminishes and there is an in crease in the capacity of the bladder and a decrease in the frequency of urination So far the results of treatment have not been of a perma

nent character but appear to be palliative One to 1.5 gm a day usually is given for a period of months or longer

Tuberculosis of Pleura, Peritoneum and Intestine—Too few cases have been studied to make any statements concerning the final results but outstanding improvement has occurred in some of the cases reported after treatment for 60 to 90 days

Summary—In summing up then, it can be said that streptomycin has a powerful effect on the tubercle bacillus and this effect is reflected in the results observed in certain forms of clinical tuberculosis This drug should be reserved for patients with a poor prognosis and for those who have an advancing lesion in spite of the usual medical treatment It is desirable to use small doses 1.0 to 1.5 gm daily for the shortest possible period of time that is consistent with maximum improvement In this way the number of reactions is reduced and the number of strains of tubercle bacilli that become resistant is likewise reduced Studies now in progress in various institutions in the United States should give additional information that will guide the medical profession in the future use of streptomycin

Streptomycin in Brucellosis

Experimental studies of brucellosis in guinea pigs showed quite clearly that when the infection is treated early that is within 1 week of inoculation and when adequate amounts of streptomycin are given daily for a period of at least 3 weeks the infection may be controlled and organisms eliminated from the body Many strains of Brucella are highly susceptible to streptomycin in vitro The results of the treatment of human infections however have on the whole been very disappointing for the reason that these organisms seem to be extremely resistant in the body It is generally agreed by those who have studied cases of acute brucellosis that no dramatic effects are observed in any case with the treatment schedules that have been employed

During treatment with streptomycin the blood often is cleared of organisms if there is a bacteremia and the temperature has returned to normal in one third of the cases There is very little evidence that the febrile phase of the disease has been shortened except in those cases in which the disease has been treated within the first 2 or 3 weeks after the onset of symptoms

The fatality rate has not been decreased so far although the total number of cases reported is small The febrile relapse rate is approxi-

mately 9 to 10 per cent in patients who have been treated The blood has been cleared of organisms in 80 per cent during treatment, although in 10 per cent of patients there has been a relapse of the bacteremia as soon as treatment has been stopped, and in approximately another 10 per cent the organisms are never cleared from the blood by 10 days to 2 weeks of treatment A dosage of 2 gm a day for periods of 2 weeks is suggested during the acute febrile phase of this disease when symptoms have been present for less than 4 weeks There is no evidence that streptomycin has had any effect on the chronic cases of brucellosis although during an acute exacerbation with bacteremia one may be able to clear the blood and to bring about a decrease in the temperature Recent studies have shown that when sulfadiazine is combined with streptomycin and continued for 4 weeks, excellent results have been obtained in the acute cases

Streptomycin in Typhoid Fever

Streptomycin has produced no dramatic effects in typhoid fever It has not decreased the fatality rate nor the relapse rate There is some suggestive evidence that in patients treated with 2 gms daily during the first 10 to 14 days of their illness the febrile period of the disease is shortened There is no evidence that treating patients after the 14th day of illness influences the disease in any way

Streptomycin in Salmonella Infections

The results in the treatment of Salmonella infections both those that produce acute gastroenteritis and those that cause enteric fever have been disappointing Occasionally one sees a temporary disappearance of organisms from the stools following the daily oral dose of 1 or 2 gm and systemic administration of 2 gm of streptomycin but the total duration of the disease does not seem to be shortened It is not clear why the results have been so unsatisfactory in patients who have an infection due to organisms that are susceptible to streptomycin in vitro

Streptomycin in Shigella Infections

A few patients with sulfonamide resistant bacillary dysentery have been treated with streptomycin given by mouth in doses of 5 gm a

day for 4 days Diarrhea and fever subsided in 12 hours and the causative organisms disappeared from the stools There is suggestive evidence therefore that certain cases of bacillary dysentery that are resistant to the sulfonamides may respond in a striking manner to streptomycin by mouth

Streptomycin in Endocarditis

Most cases of bacterial endocarditis are due to gram positive microorganisms that are sensitive to the action of penicillin There are a few cases due to gram negative bacilli or to organisms that are penicillin resistant and streptomycin sensitive Such cases have been studied especially by Hunter at the Presbyterian Hospital in New York City On the basis of the experience reported by him streptomycin should be given a trial in all infections due to gram negative bacilli or to penicillin-resistant gram positive cocci and in infections that have failed to respond to penicillin therapy

The dosage recommended by Hunter is 2 to 6 gm a day for a period of 2 to 4 weeks depending on the sensitivity of the organism and the clinical response In occasional cases of endocarditis caused by microorganisms that show in vitro sensitivity to both penicillin and streptomycin a course of therapy with both drugs together has been used with success It should be emphasized that when large doses of streptomycin are given such as 4 to 6 gm a day for 2 to 4 weeks neurological symptoms are likely to occur Some patients may even develop deafness and for this reason audiometer and vestibular function tests should be done at regular intervals during treatment

Streptomycin in Peritonitis

The outcome in any group of patients with peritonitis will of necessity depend on a number of factors aside from chemotherapy However, inasmuch as most cases of bacterial peritonitis are due to organisms that commonly inhabit the gastro-intestinal tract are gram negative in type streptomycin has been tested in a wide variety of cases of peritonitis due to various primary causes When peritonitis is produced experimentally in animals it has been shown that the fatality rate can be reduced by giving streptomycin Further improvement is observed when both penicillin and sulfonamides are added to the streptomycin

From a study of 203 cases of peritonitis reported to the Committee on Chemotherapy of the National Research Council it was apparent that streptomycin is useful in the treatment of patients with bacterial peritonitis The best results were observed when the peritonitis was localized near the site of the infection and more favorable results were observed in the cases of generalized peritonitis without other complicating infections than when complications were present in areas remote from the site of the original infection

The prognosis is more favorable in patients under 20 years of age and in those patients who had been ill for less than 2 weeks when streptomycin was started The outlook is improved when the infection is due to a single gram negative organism or to a mixed gram negative infection than when there is a mixed gram-positive and gram negative infection Streptomycin often controlled invasive infections and assisted in the control of the local infection Optimal results were obtained when 2 grams a day were continued for 10 to 14 days

In generalized peritonitis permanent improvement occurred in 74 per cent of cases when the peritonitis was localized, improvement attributed to streptomycin resulted in 9 per cent when the peritonitis was generalized and there was an associated infection remote from the original source (subphrenic abscess, empyema, liver abscess, etc), improvement occurred in only 45 per cent of patients

It is recommended therefore, that streptomycin should be given to all patients with peritonitis Also, patients should receive penicillin and sulfadiazine since the infection commonly is a mixed one

Streptomycin in Wound Infections

The treatment of established infections of wounds is a complicated procedure The use of penicillin and the sulfonamides will prevent invasive infections due to susceptible organisms in wounds These drugs aid in the sterilization of local foci of infection Sooner or later gram negative bacilli appear in all chronic infected wounds and they may dominate the bacteriologic flora There are those who hold that gram-negative bacilli do not interfere with the healing of wounds but the studies of Howes stress the fact that they definitely do so Howes has also presented good experimental evidence that streptomycin can be given topically to rid wounds of persistent gram negative bacilli when no slough is present

On the basis of these observations it can be said that a solution of streptomycin in a concentration of oo mgm per cubic centimeter can be used in freshly wounded tissues without further damage and that wounds heal without delay Furthermore it has been shown that granulations are not damaged by 1 000 units of streptomycin per cubic centimeter Streptomycin, then can be said to be the best non toxic antibiotic that has been discovered so far for destroying gram negative bacilli

It has been recommended that penicillin in concentrations of 1 000 units per cubic centimeter or 5 per cent sulfamylon should be combined with streptomycin when it is used topically The purpose of this combined chemotherapy is to assist in the killing of susceptible bacteria of both the gram positive and gram negative groups As adjuvants to therapy when slough is present Howes has demonstrated that resolution of the established localized infection can be hastened b the use of chemicals that will liquefy slough and permit antibacterial substances to penetrate and kill the bacteria that remain

Streptomycin in Infections of the Biliary Tract and Liver

Cholangitis —Infections of the biliary passages due to gram negative bacilli with or without bacteremia are controlled in 90 per cent of cases The blood is cleared of organisms when bacteremia is present and the temperature is reduced in all patients who improve Streptomycin is a valuable adjunct to surgical treatment when it is used The local focus often is sterilized or the drainage is decreased The recommended dosage is 1 to 3 grams a day for 7 to 10 days

Acute Cholecystitis —The patients in whom streptomycin has been most effective in acute cholecystitis has been those with bacteremia and those with peritonitis It was a useful adjunct to surgical drainage The dosage is 1 to 2 grams a day for 7 to 14 days

Pylephlebitis —This serious disease of the liver may be controlled in 60 per cent of cases when the organisms causing the infection are *E coli* or *Ae aerogenes* In the cases studied by the Committee on Chemotherapy bacteremia was present in all cases prior to treatment Streptomycin should be given daily for 1 to 3 weeks in amounts of 2 to 3 grams

Streptomycin in Miscellaneous Diseases

Cholera.—Streptomycin has been used in the treatment of a few patients with cholera. It was given by mouth in doses of 4 gm a day along with an occasional intravenous injection. There is no clear indication that it had any advantage over large amounts of fluid and the sulfonamides. It is true, however, that the number of cholera vibrio diminished in the stools following treatment, although some were still present there and had increased in resistance.

Infections of the Eye.—Corneal ulcers due to *Pseudomonas aeruginosa* and *Escherichia coli* have been treated successfully by a streptomycin solution instilled into the conjunctival sac. *Ps aeruginosa* ulcers of the cornea are always serious and difficult to cope with, so that streptomycin should be used in all such cases. Solutions of 1,000 units per c c should be used locally.

Infections of the Ear.—Infections of the middle ear due to gram negative bacilli have responded well in the few cases that have been treated. *Ps aeruginosa* infections of the middle ear and mastoid do not respond well to streptomycin alone, and surgical treatment is needed along with chemotherapy, if satisfactory results are to be obtained.

Streptomycin has been used locally for the treatment of chronic otitis media or otitis externa when the organisms belong to the gram negative group. Instillations of streptomycin solution in 20 mgm per cubic centimeter of physiological saline solution four times a day are used. For the local treatment of otitis externa wicks saturated with streptomycin solutions of . 5 to 5 mgm per cubic centimeter are applied locally.

In all of these cases other treatment may be necessary.

Localized Abscesses.—Streptomycin has been employed in the treatment of a variety of abscesses due to gram-negative or mixed infections. These include peri appendiceal, ovarian, subhepatic, subphrenic tubo-ovarian and ovarian, liver, perirectal and retroperitoneal abscesses. In many instances these abscesses are complicated by other intra abdominal lesions, and in some bacteremia has been present. Surgical treatment has been employed in many so that the streptomycin is only adjuvant treatment. It can be said that between 60 and 85 per cent of patients show improvement following the use of streptomycin. This is reflected in a change in the course of the disease, a decrease in the amount of drainage from the abscess, a diminution or disappearance of bacteria from the

local focus of infection and a clearing of bacteria from the blood when bacteremia is present

Prompt treatment with 2 grams of streptomycin daily given in two equally divided doses of 1 gram each for 10 to 14 days or longer depending upon the course of the disease and the response of the patient to *treatment, is the minimum*

Ulcerative Colitis—Streptomycin has not influenced the uncomplicated course of ulcerative colitis Occasionally when bacteremia complicates the illness or when there is a perirectal abscess streptomycin has proved to be beneficial in controlling these complications

Diverticulitis—*All patients with attacks of diverticulitis and signs of* localized peritonitis or abscess or bacteremia should receive streptomycin The dosage schedule that has been beneficial has been 2 grams for 5 to 14 days

Epidemic Diarrhea of Newly Born—This disease, of unknown cause probably viral in origin *has not been influenced favorably by* streptomycin when it is given either by mouth or intramuscularly

Postabortal and Puerperal Sepsis—In postabortal and puerperal sepsis due to gram negative bacilli the course of the disease can be profoundly altered by using streptomycin That is to say in 80 per cent of cases *the bacteremia is cleared the temperature returns to normal* within 3 to 6 days and the constitutional symptoms and signs of infection regress All patients with this type of infection should receive 2 grams of streptomycin daily for 10 to 14 days

Granuloma Inguinale—This disorder due to Donovan bodies has *responded in a striking manner to streptomycin It should be* given as soon as the diagnosis is established The recommended dosage is 4 grams a day for 5 days

Syphilis—It is doubtful if streptomycin will prove to be useful in the treatment of human syphilis In the rabbit it has been demonstrated that *streptomycin has antisyphilitic action but penicillin G* is more than 3 000 times greater A few patients with early syphilis have been treated with streptomycin with a total dosage varying from 1 to 10 million units In three negative dark field examinations were obtained within 1 to 8ι hours but subsequently all patients relapsed

Gonorrhea—Streptomycin has been *effective in* the treatment of gonorrhea A few cases have been treated successfully following the injection of 0 2 gm in a single injection In case of failure on this dosage schedule cure usually is obtained when a second injection of 0 2 gm of streptomycin is used

Plague—From experimental studies in animals streptomycin has a powerful effect in *P pestis,* so that it should be employed in all cases of human plague in an attempt to determine whether it will affect the course of the disease

Anthrax—The anthrax bacillus is sensitive to streptomycin In any case of anthrax that should fail to respond to penicillin, streptomycin should be used

Diseases in which Streptomycin is Ineffective

A wide variety of diseases have been treated with streptomycin without benefit A list of them is included below

- Actinomycosis
- Exfoliative dermatitis
- Infectious mononucleosis
- Panniculitis
- Poliomyelitis
- Rat bite fever
- Rheumatoid Arthritis
- Rhinoscleroma
- Reiter's disease
- Typhus fever

Prophylactic Use of Streptomycin Before Operations on the Large Intestine

Zintel and his associates at the University Hospital in Philadelphia have shown that the oral administration of streptomycin reduces the total population of bacteria in the feces They have used the drug therefore, in doses of 1 to 2 gm a day preoperatively, and streptomycin and penicillin postoperatively in all patients operated on for resection of the large intestine A greater number of such resections can be done with primary suture, and the chances of peritoneal infection are reduced, if streptomycin is employed in this way

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CHAPTER XXXI

THE COMMON COLD

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Definition

The common cold is an acute inflammation of the upper respiratory tract, chiefly of the nasal mucous membrane, which manifests itself by local and by more or less disagreeable constitutional symptoms. Its etiology is as yet undetermined. The condition occurs most frequently during the winter months and in regions of temperate climate where large numbers of the population are affected almost simultaneously. The attacks are sudden in onset and are ushered in by sensations of general coldness or chilliness. Sneezing and profuse watery nasal discharge occur early, followed by thickening of the discharge and stuffiness of the nose which interferes with breathing. The duration of an attack is from three to five days or longer, and remission is gradual. Complications, mainly sinusitis, pharyngitis, tracheitis and bronchitis, usually prolong the course. An attack confers no lasting immunity; in fact, most persons are afflicted several times during a year, although a few have attacks less frequently or not at all.

The synonyms chiefly in use by the layman are cold, cold in the head, acute cold and catarrh or acute catarrh. Catarrh (Greek, *I flow down*)

is inflammation of any mucous membrane by popular usage now reserved for that of the nasal passages unless otherwise specified as in bronchial catarrh , catarrh of the bowels etc

The synonyms in use by physicians are cold cold in the head coryza or acute coryza (Latin from Greek *catarrh*) and rhinitis or acute rhinitis (Latin *inflammation of the nose*) The terms hyperesthetic rhinitis and vasomotor rhinitis are reserved for hay fever allergic rhinitis whereas atrophic rhinitis refers to ozena

On the other hand the term common cold and its synonyms have become more or less generic and are applied erroneously to a number of conditions Influenza allergic rhinitis or hay fever sinusitis and the rhinitis that precedes certain infectious diseases are the conditions that are thus misnamed most commonly Such errors occur both because of ignorance of the public and because of mistakes in diagnosis made by the physician The confusion that exists has been described by Cheney[1] who says The layman uses the term a cold to cover a multitude of conditions which even the medical man does not always differentiate viz an acute coryza rhinitis pharyngitis laryngitis bronchitis la grippe influenza and sometimes tonsillitis However such a state of affairs is to be expected when the etiology of a disease or group of diseases still is a matter of doubt

History

The common cold because of its very nature as well as the evidence that written records have left to us must have had its roots in antiquity The ancient Greeks familiar with the condition ascribed it as they did most diseases to the effects of the various elements earth air fire and water These in combination with the four qualities dry cold hot and moist were believed to exist in balance with the four humors of the body Any disturbance of this balance resulted in disease This concept came into being over a period of time and was as much philosophical as physiological in origin Nor was the hypothesis static it was modified constantly as successive generations of men made observations and attempted to explain them

Hippocrates (circa 450 B C) in Epidemics I and II included reports of several cases that in modern times have been diagnosed by authorities as common colds with and without fever In the Aphorisms also he mentioned the common cold several times There is an interesting reference to this condition in the chapter on *Ancient Medicine* In the first place those of us who suffer from cold in the head with discharge

from the nostrils generally find this discharge more acrid than that which previously formed there and daily passed from the nostrils it makes the nose swell and inflames it to an extremely fiery heat as is shown if you put your hand upon it And if the disease be present for an unusually long time the part actually becomes ulcered although it is without flesh and hard But in some way the heat of the nostril ceases not when the discharge takes place and the inflammation is present but when the running becomes thicker and less acrid being matured and more mixed than it was before then it is that the heat finally ceases But in cases where the evil obviously comes from cold alone unaccompanied by any thing else there is always the same change heat following chill and chill heat and these supervene at once and need no coction In all other instances where acrid and unmixed humours come into play I am con fident that the cause is the same and that restoration results from coction and mixture

Galen (circa 150 A D) gave added weight and new impetus to the old humoral hypothesis of the cause of the common cold Celsus at the be ginning of the Christian era and contemporary with or a little later than Galen knew of the common cold He although not a physician wrote more or less popular works on medical subjects for the laity In a dis cussion of colds in De Medicina[3] he stated Sometimes there is a humor discharged from the head into the nose which is only a slight inconveni ence sometimes into the fauces which is worse sometimes even into the lungs which is the worst of all If it have dropped down into the nostrils a slight discharge takes place from them a slight pain is felt in the head with a sensation of heaviness and sneezings are frequent If upon the fauces it initiates them and excites a slight cough If into the lungs besides the sneezings and cough there is also a heavine s of the head lassitude thirst heat and bilious urine

But a gravedo although it does not differ much is nevertheless another disease This obstructs the nostrils renders the voice obtuse and excites a dry cough at the same time the saliva is salt there is a noise in the ears the veins of the head are excited and the urine is turbid Hippocrates named all these affections CORYZAE I observe that this term is now applied by the Greeks to gravedo and catarrhs are called by them castagmi

It would be pointless at this time to trace the history any further except to cite one example of the persistence of ancient ideas despite medical advance To quote Dorland[4] The ancient belief that catarrh resulted from a flux from the brain had firmly ingrafted itself upon the medical mind and died very hard Even at the zenith of the age of

reason — the reign of the English Queen Anne — James Handley a popular writer on health remarks Fernelius saith besides serum within the cranium there s other excrements gathered in the external parts of the head especially under the cutis of the vertex where the vessels have their extremities which when they grow turgid with too much serum or other humour they shed forth under the skin that which they cannot carry off and there it remains because the thickness and looseness of the cutis permits it not to evaporate and there s sometimes so great a collection here that it causeth a soft swelling that manifestly heaves up the pericranium from the cranium This is assuredly the source of all external distillation Hence rheumes fall into the eyes cheeks teeth neck shoulder blades sides back loins hips thighs and all the joints and this is certainly the foundation of every external pain particularly in a catarrh It was to clear the brain of rheumes and humours that the habit of taking snuff originated — and this after sixty five hundred years of medical scientific growth!

This ancient conception is still evident in words of modern Continental European languages as well as in the English word rheumatism

French	Cold in one s head	*rhume de cerveau*
	Cold in one s chest	*rhume de poitrine*
	To catch cold	*attraper un rhume prendre du froid*
German	Cold	*die Erkaltung der Schnupfen*
	To catch cold	*sich erkalten den Schnupfen bekommen*
Spanish	Cold in the head	*romadizo catarro*
	To catch cold	*resfriarse*

Just how the word cold became related to the condition to which it is applied is not known though Hippocrates and later writers all mention exposure to cold as one of the exciting causes The term is now so firmly ingrained in usage that it seems unlikely that it will ever be supplanted Attempts have been made occasionally to change the descriptive term common cold to something more appropriate and to find a scientific or medical synonym Most of the new terms suggested reflect the etiology which is suspected or believed to be true at that particular time Spriggs and Millard in 1919 wrote we think by far the most important step in the educational line is to adopt a proper name for this class of infection As long as a definitely infective condition is called a cold or a chill by the doctor it will quite naturally be treated by the patient as if due to a cold that is he will wrap up (probably too much)

shut up the windows and so unconsciously do his best to spread infection to the rest of the household This line of treatment has been seen in numberless cases in the recent epidemic with disastrous results But we would go further and say that as long as the view of the patient that his condition is due to chill or cold is acquiesced in by his doctor or as long as the latter tolerates the designation cold (and we quite realize how very easy it is so tacitly to agree with one s patient) there will be no real educational progress in such matters

In bulletins about the health of distinguished personages we are frequently informed that So and so is suffering from a severe chill or a bad cold etc Surely it would be better to say a pyrexial attack or acute nasal catarrh if such are meant

The correct term for a heavy cold in the head extending from nose to larynx would be we suppose acute infectious nasal nasopharyngeal and laryngeal catarrh but this would obviously be too cumbersome it might be abbreviated to infective catarrh perhaps or even some shorter term coined

The term coryza has much to recommend it being short and non committal But as this term does not cover a laryngeal catarrh we think it is not entirely suitable

It is safe to assume that until the etiology is determined the present term will persist and that very likely even then no substitute will be accepted The appellation is too descriptively suitable and certainly too time honored to be discarded

THE STRUCTURE AND PHYSIOLOGY OF THE NOSE

The nasal passages constitute the normal pathway for inspired and expired air secondarily they contain the organs of smell In transmitting air their main function is that of a barrier between the variable temperature and humidity of the atmosphere and the constant relatively high temperature and humidity of the delicate pulmonary structure Were it not for this function the nasal passages could be simply straight tubes instead they are of complex construction adapted to provide the greatest possible tissue surface to the incoming air

The left and right nasal passages are formed by the septum which extends from the external nares to the posterior choanæ Three horizontal channels are formed on either side by the superior middle and inferior turbinates which project in from the lateral wall not quite to the septum and extend from the vestibule to the nasopharyngeal meatus

The mucous membrane that lines the entire cavity and which extends

into and lines all the sinuses is densely adherent to the bone and cartilage It joins the skin at the external nares the mucous membrane of the pharynx at the choanae and the conjunctivae at the lacrimal ducts Its structure in different areas varies with its function It is modified into olfactory mucous membrane over the superior turbinates and the upper third of the septum It is very thin over the floor of the nose and in the various sinuses It is thick over the septum but of greatest thickness and most vascularity where it covers the superior, middle and inferior turbinates

The superficial layer of the mucous membrane is composed mainly of columnar and ciliated cells among which lie goblet or mucin cells beneath this is a fibrous layer rich in lymph channels and farther beneath an almost continuous layer of glands both mucous and serous whose ducts open on the surface Mucus which is a secretion continuously produced by the entire mucous membrane is of watery consistency and becomes viscid by evaporation Cilia form the motor mechanism of the nose propelling mucus and foreign matter such as dust bacteria etc backward into the nasopharynx

The turbinates covered by spongy highly vascular erectile tissue with many mucus secreting cells and glands are highly important organs of respiration It is their function to warm the inspired air and to add moisture to it This is accomplished by increase in turgescence of the turbinates the colder the air the greater the erection Thus theoretically air reaching the lungs after passage through the nose is of constant temperature and humidity This is true within a wide range of atmospheric temperature though naturally air at a temperature higher than that of the body cannot be cooled while very cold air cannot be warmed sufficiently For this reason the turbinates are very sensitive to variations in atmospheric temperature and to a lesser degree to changes in humidity This sensitivity is evident in the transient rhinorrhea produced by breathing very cold air or that occasionally produced by drinking very hot liquids

The mechanism by which turgescence is produced was not understood exactly until Burnham[6] made an extensive anatomical investigation of the course of the arteries and veins that supply the nasal mucous membrane This had been done first by Zuckerkandl in 1884 but little attention was accorded his work until Burnham s recent and more exact study was made It has been demonstrated that the veins from the turbinates at several points travel through bony canals which being rigid permit passage of only a certain volume of blood In fact the diameter of the vein in the canal is less than that of the confluent veins entering it so that

Burnham called these places bottle neck constrictions He states The erectile (cavernous) tissue contains a large volume of blood when fully dilated It is comparatively superficial extremely sensitive to external stimuli and subject to rapid contraction These bottle neck constrictions may therefore be the means of causing considerable hindrance to the circulation and an interesting chain of reactions would then result Thus these anatomical findings have introduced an important factor in the explanation of the cause of the intumescent turbinate

A second function of the turbinates together with the vibrissæ in the vestibule is to act as filters As such they are the first line of defense in the air passages Thomson[7] has shown that through the trapping action of the moist sticky mucus and the motile power of the cilia in removing this secretion practically no bacteria or particles of dust reach the nasopharynx through the nose

Pathology

Very few examinations have been made of the nasal mucous membrane during attacks Because the condition is not fatal opportunity for examination is rare The first pathologic study seems to have been made by Mackenzie[8] who found intense engorgement of the mucous membrane particularly of the inferior turbinates There was an increase of lymphoid cells and some fibrinous exudate was present Mackenzie s observations were made on only two patients one of whom had died in uremia with a nasal condition similar to that occurring in acute coryza Hilding[9] more recently has observed the histopathological condition of the nasal mucous membrane in acute colds He states The pathologic process is that of a mucous membrane inflammation showing rather marked tissue changes including the loss of many of the surface cells and a proliferative reaction in the submucosa The epithelium is regenerated and repaired by the growth and multiplication of the stellate cells normally found deep in the epithelium His report was based on study of biopsy specimens from 25 patients and mucosal scrapings from 100 additional patients with acute common colds

Long Bliss and Carpenter[10] as well as Hilding have studied the changes in the cellular content of the secretions Early in the course of the disease few cells are found but ciliated epithelial cells appear late in the first day and become more numerous on the second day Late in the second day appear deeper epithelial cells and polymorphonuclear cells which later constitute nearly the entire cellular content of the secretions Occasionally polymorphonuclear cells alone predominate in all stages

Kahn and Stout[11] investigated the cytologic changes of the nasal discharge in 97 cases of infection of the upper respiratory tract, 87 of which were allergic In 73 proved cases of hay fever the nasal discharge of 50 patients showed 10 to 90 per cent eosinophils that of 9 patients showed 3 to 10 per cent eosinophils and the secretions of 14 patients showed none although in 5 of these cases eosinophils were found on re examination In the 10 non allergic cases of acute or chronic upper respiratory tract infection no eosinophilia was present in the nasal smear It is interesting that in later study of the secretions of 10 patients with hay fever accompanied by colds these authors found that the previous eosinophilia in most instances extreme had been replaced completely by a purely non eosinophilic polymorphonuclear cytosis the eosinophils having disappeared for the time being In the secretions from 17 other patients from 5 to 40 per cent of eosinophils accompanied the non eosinophilic polymorphonuclear cytosis

EPIDEMIOLOGY

The common cold is a sporadic affliction which becomes epidemic at certain times of the year The word epidemic (Latin epidemus *among the people*) is used here advisedly to mean of high incidence in the population it does not imply that the disease is due necessarily to infection by a living agent Frost[1] has pointed out that a fundamental difficulty in studying the common cold is the inability to identify a clinicopathological entity which is pathognomonic This places limitations upon both experimental and epidemiological studies Frost says For epidemiological investigation a primary requirement is to mark off for study a clinical unit so distinctive as to justify the presumption that it coincides with an etiological unit Thus little of specific value can be said concerning the epidemiology of a disease whose etiology is not known definitely There is much information in the literature which contributes to the subject but which requires critical analysis rather than acceptance at face value Observations of a pseudo medical nature also have been made chiefly by Arctic explorers A large amount of word of mouth information is available but very little of it has been reported carefully

Perhaps the best known and most widely quoted legend is that of the Island of St Kilda The few inhabitants were isolated from the world except for the occasional landing of a boat at which time they all developed cough and coryza This has been cited as a clear cut example of the transmissibility of colds despite the fact that as Boswell in his

famous biography of Johnson quoted The situation of St Kilda renders a North East wind indispensably necessary before a stranger can land The wind not the stranger occasions an epidemic cold

Paul and Freese[13] in 1933 reported their study of such a situation in Spitsbergen Here also local history has it that epidemics of colds never occur before the first ship arrived in the summer and that this epidemic is never escaped though the severity and rate of attacks vary from year to year The authors reported that the cold epidemic during their study began 48 hours after the first ship arrived and reached its peak 4 to 6 days later They found no particular variation in atmospheric conditions which could account for the epidemic

It must be admitted that the case for contact infection is a strong one Arctic explorers almost uniformly report freedom of their men from infection until they return to civilization when many come down with colds They also report a high incidence among Eskimos after contact with strangers Heinbecker and Irvine Jones[14] reported the findings of the Greenland Expedition in the summer of 1926 As they went up the coast they noted a high incidence of acute upper respiratory diseases in certain villages whereas others seemed free of such diseases Investigation showed that the residents of the former villages had had contact with the outside world prior to their coming In the villages free from respiratory diseases 48 to 72 hours after their arrival all the natives developed acute respiratory infections with sneezing coughing and spitting Even though no member of the expedition might have an acute respiratory infection the malady would appear among the natives When they revisited these villages three or four weeks later they found that in some of them the infection had subsided while in others it was still present but abating They stated Physical examination of persons suffering from these acute respiratory tract infections showed a moderate elevation of pulse and temperature reddening and swelling of the mucous membrane of the nose and pharynx with a mucopurulent exudate occasionally slightly blood tinged The lungs gave the signs of a diffuse bronchitis

An example of contact infection under controlled conditions has been reported by Long and his co workers[15] They reported two colds which occurred in a colony of 9 apes presumably contracted from a laboratory worker who had been making throat cultures from members of the colony The apes were kept in isolation cages and all who came in contact with them wore gowns and masks The one ape was visited in the morning the other in the afternoon at which times the observer entered the cage but neglected to adjust her mask over her face The observer developed

a common cold 24 hours after visiting the colony the two apes 48 hours after the visit The authors concluded that the common cold is infectious in the incubative stages and that masking does not afford much protection

It is believed also that colds may be spread by fomites There is the classical example of Shackleton s arctic explorers who were infected not through exposure to extreme cold and wet but by opening bales of clothes which had been packed in London Newspapers recently carried stories of such an occurrence among Byrd s men at Little America in the Antarctic Many have believed it possible that food contaminated by an individual with a cold may be a vector Bliss and Long[16] tested this hypothesis with studies on a colony of 15 chimpanzees The animal having had no colds for two months were placed under isolation conditions for seven days at the end of which time an individual suffering from a common cold in the second day of its course prepared three meals for the animals The individual came in contact with neither the animals nor the attendants Within 48 hours 5 of the 15 apes developed typical common colds The authors concluded that experimental proof had been advanced of the common belief that colds can be transmitted by food

Several observers approaching the problem from the statistical standpoint have obtained records at from weekly to monthly intervals of colds occurring in large groups of individuals Some of these surveys have been continued for several years or longer For several reasons it is dangerous to reach too many definite conclusions from such statistical surveys The diagnoses usually are made by lay subjects and are based on indefinite groups of symptoms the points of differentiation between a cold and hay fever are not common knowledge epidemics such as of influenza tend to confuse the diagnosis with that of other respiratory diseases and the complete co operation of many scattered individuals not under direct observation is impossible to obtain However these surveys if large enough do yield items of information of distinct value

The United States Public Health Service[17] sent bi monthly questionnaires to 13 000 persons mainly college students in 11 localities scattered *from Massachusetts to California* *Various data were asked for* particularly concerning the onset of acute respiratory diseases They found that The most striking indication afforded by these graphs is the synchronous behavior of the incidence of respiratory affections in all of the localities plotted The high incidence in the latter part of October was followed in all of the localities by a decline which continued until the latter part of December then a sharp rise occurred which in all of the localities save one reached its peak in the first part of Janu

ary a period of only one half month this was followed by a gradual decline in the incidence in nearly all of the localities until the end of the period under consideration There occurred also minor peaks throughout the year particularly in the winter months No means were available to differentiate colds from epidemic influenza

Other information of value has been derived by statistical analysis of reports of surveys Frost and Gover[18] prepared tables from the Townsend and Sydenstricker reports[19] mentioned later to study the infectivity of colds They conclude One of the most striking of the facts presented in this table is that in each period incidence was materially less among families than among students This difference is not satisfactorily accounted for by the special age distribution of the students nor does any difference in geographic distribution seem to be a sufficient explanation It is noted in this (another) table that in each period the incidence of influenza is higher in the family group than in the student group as a whole whereas the reported incidence of all respiratory diseases is materially higher in the student than in the family group Perhaps a new light has been shed on these findings since it is now known that influenza is a virus disease and is highly contagious A corollary would be that the common cold is either much less or not at all infectious but no proof of this can be deduced from their findings

The burden of proof rests on those who would hold that the common cold is an infectious disease The investigations in various Arctic or isolated communities were carried out on the assumption that a living agent was the etiological factor and thus that the observations made supported this hypothesis The wish easily may have been father to the thought Had all these investigators approached the problem with the idea that change in atmospheric temperature was the etiological factor then it is not unlikely that all the observations made would have been explained on this basis Careful analysis of the St Kilda legend and the more recent report of Paul and Freese from Spitsbergen give clear evidence of seasonal temperature variation constant from year to year and of sufficient degree to permit explanation of the cold outbreaks on this basis The relationship however is neither sufficiently clear cut nor definite enough to warrant change in the original hypothesis which is quite fair The regrettable part is that the weight of contradictory evidence is neglected thus discouraging further research on a problem which is considered solved We may yet see the day when the words quoted by Boswell The wind not the stranger occasions an epidemic cold will emerge from their present obscurity

There remain still the numerous observations on men returning from

Arctic exploration free from colds until they reach civilization and the reports of cold epidemics among Eskimos free from infection until civilization reaches them Of the latter the work of Heinbecker and Irvine Jones[14] with the Greenland Expedition is an example and their investigations were more extensive and careful than many Here the contradictory evidence is of a somewhat different nature Careful analysis of the report brings out the fact that the epidemic among the Eskimos occurred whether members of the expedition had colds or not that the physical examination gave the findings of a pyogenic infection that the Eskimos rarely have pyogenic skin infections yet are susceptible to them by skin test Consequently whether it be long isolated explorers returning to civilization or visitors from the outside world invading long isolated communities the likelihood of pyogenic infection picked up from the population being the explanation of the consequent acute upper respiratory attacks had been overlooked In the case of the Eskimos the definition of a common cold has to be stretched somewhat to include the picture seen and one wonders if this has not been true as regards the explorers also Once again the facts have been forced to fit the hypothesis which in the long run may not prove to be incorrect but which at the present time omits from consideration the contradictory facts Comments upon experimental studies in animals will be made in the section on Etiology

Etiology

The common cold is known to be the most frequently occurring and the most economically wasteful disease affecting the populations of temperate climates Because the disease does not result in serious incapacity scant attention has been paid to it in the past However in the present highly industrialized age it is attracting increasing attention because absence from work and inefficiency of workers result in considerable financial loss

The hypothesis that the common cold is a highly contagious disease is accepted generally but this conception is supported by inadequate scientific data Previous to the discoveries of Pasteur and for some time thereafter emphasis was placed upon exposure to chilling fatigue and indiscretion in diet as etiologic factors With the growth of bacteriological knowledge bacteria were incriminated as the cause of many diseases that are now known not to be caused by bacterial agents e g pernicious anemia beriberi cancer Hodgkin s disease leukemia conditions occurring in outbreaks of epidemic proportion caused by lead arsenic and other mineral poisons and diseases such as epidemic and endemic goiter

almost certainly due to iodine deficiency The bacteriological field has been explored widely and with the methods now available for study few discoveries remain to be made Students of other branches of biology and of medicine have found that many diseases formerly considered of infectious origin have causes other than invasion by bacteria or protozoa Studies in the physical and chemical fields have provided abundant examples of disea es caused by physical and chemical agents or by lack of them New light has been thrown on the functions in health and disease of the endocrine glands and of the autonomic nervous system The reactions of the tissues to allergic agents have been demonstrated These and many other additions to our knowledge made in recent years have called attention to the fact that our environment is an universe with not one but many major sources of danger to the individual The old conception that homeostasis was jeopardized by only living things seen and unseen must now be modified to include hazard from physical influences as well

Statistical methods have been used to study the characteristics of the disease Attempts have been made to study the incidence rate of attacks their relation to changes in the weather and other possible causative factors The United States Public Health Service and the health services of large industrial organizations have made contributions to our knowledge of the subject From an analysis of published reports and from our own experience it may be stated that no statistical survey based upon inadequate diagnostic criteria and with inadequate co-operation on the part of the subjects of the study can in the final analysis be of any great value The seasonal incidence of the disease suggests that meteorological changes may have an important bearing upon the initiation of the attack but with the data at hand a causal relationship cannot be established

During recent decades in studies on the common cold an effort has been made to discover the causative agent in the nose and throat Hunter[79] in 1873 described a micro-organism as the etiological agent in coryza Thereafter each of the bacteria found in the nasal passages during colds similarly was incriminated either alone or in combination with others until the list included the various strains of staphylococci streptococci and pneumococci *Micrococcus catarrhalis* the diphtheroid group and Pfeiffer s bacillus (*B influenzæ* or *Hemophilus influenzæ*) In contradiction however it was early reported that the bacteria frequently were found to be reduced in number or absent in the early stages of a cold and increased in number only during the later stages Various workers found it impossible to produce colds by inoculation of these bacteria Bloomfield[1] studied the normal bacterial flora of the noses and throats of individuals over a period of months and observed the changes that occurred when a

cold or a throat infection developed He found no bacteria in the cultures from an early cold to which a causative role could be assigned Dochez and his co workers[22] corroborated this work They reported that bacteria were scant or absent in cultures taken early during a cold though late in the course certain organisms became prominent as secondary invaders usually *Staphylococcus aureus* *Streptococcus hemolyticus* and the *B influenzæ* (*H influenzæ*) They agreed with Bloomfield that no bacteria had been found to which a causative role could be assigned Today there are few advocates of the hypothesis that any of the bacteria ordinarily present in the nose play a primary role in causing the disease The most prominent champions are Thompson and Thompson[23] who are very definite in their statements to this effect in their monograph They present excellent photographs of cultures but give very scanty experimental data as a basis for their conclusions

In 1914 Kruse[4] ascribed the etiology of the common cold to a virus He had diluted with saline solution the secretion from the nose of an assistant suffering from a cold This material was filtered through a Berkefeld filter then several drops were instilled into the noses of 12 men In from 1 to 3 days 4 33 per cent of the volunteers developed typical colds Kruse later repeated this experiment this time with 36 students as volunteers Within 1 to 4 days in the majority of instances within 2 to 3 days 15 students 42 per cent developed colds He stated that during the same period of time only one cold occurred among 29 students and 7 assistants who had not been inoculated this he considered an adequate control Kruse named the virus *Aphanozoum coryzæ* the generic name being derived from the Greek terms for *invisible* and *animal*

The work of Kruse was confirmed by Foster [26] in 1916 and 1917 who inoculated 10 volunteers with a Berkefeld filtrate of the nasal secretion from three subjects with colds Three to 6 drops of the material were allowed to ascend each nostril by gravity the head being tilted back Of the 10 persons inoculated 7 developed clear cut and definite symptoms of acute coryza 2 had questionable symptoms and one had none The incubation period was 8 to 30 hours Foster then attempted to culture the infective agent using the Noguchi method This method is anaerobic and the culture material is tissue ascites fluid He discovered coccoid bodies of minute size which he suggested might be the infective agent Eleven volunteers were inoculated with material from the second generation subculture of his cultures All developed colds though one was mild From the nasal secretions of these individuals with colds experimentally induced he was able again to culture and to subculture the minute micro organism

Olitsky and McCartney[7] accomplished the transmission of colds in the early stages to a very small group using filtered nasopharyngeal washings. Employing blood agar plates and anaerobic technique they were able to culture three groups of anaerobic filter passing Gram negative bacteria previously described by Olitsky and Gates.[8] These are very likely the organisms which were first reported by Foster [6] as minute coccoid bodies. Olitsky and Gates ascribe no significance to them because of the irregularity of their occurrence in the nasal secretions from subjects with colds, influenza patients and supposedly normal individuals. This group of organisms is not to be confused with a very similar organism *Bacterium pneumosintes* implicated by Olitsky and Gates as the etiological agent of influenza.

Several workers have reported negative results using the Berkefeld filtrate inoculation technique. The first of these was Schmidt[9] who in 1920 made 196 instillations of supposedly infective material into 16 volunteers. Only 25 colds developed, 12 per cent, of which 3 were reported as being influenza. With 43 control instillations 8 colds developed, 19 per cent. Williams and her co-workers[10] using Foster's technique were unable to corroborate his culture findings. They reported also that using the filtrates of secretions from 7 subjects with early colds and 3 with influenza they were unable to reproduce any symptoms in 45 human volunteers. Robertson and Groves[31] in 1924 demonstrated the coccoid bodies of Foster in Berkefeld filtrates of cold secretions. However, of 100 volunteers 95 developed no symptoms and there was one case each of bronchitis, coryza and influenza, and there were 2 of laryngitis. This, they say, is not any greater an incidence than is found normally in the population.

The two groups of investigators who have investigated most extensively the virus hypothesis and who have advanced it to its present prominence are Dochez and his co-workers in New York and Long and his co-workers in Baltimore. These investigators, working separately, have corroborated the research of Kruse and Foster, using as experimental subjects both man and apes and reaching their conclusions almost simultaneously.

Dochez and his group having disposed of the bacterial hypothesis as already mentioned, then studied the Gram negative filter passing anaerobic organisms described by Olitsky and Gates and by Gates and McCartney but found[3] that they constitute part of the normal flora of the upper respiratory tract and as such bear no relationship to the common cold. The group next reported[32] that they were able to produce in apes by the inoculation of Berkefeld filtrates of nasopharyngeal washings

from individuals with colds a condition which bore a striking resemblance to the human disease In all of the positive experiments however the bacillus of Olitsky and Gates appeared in the cultures To rule out this organism as a factor apes were inoculated[34] with the Berkefeld filtrates of the nasopharyngeal washings from normal individuals No colds occurred though the organism appeared in 75 per cent of the cultures made from the filtrates These findings were confirmed by Long and Muellerschoen[35]

In 1930 Dochez Shibley and Mills[36, 37] published the results of their work on the experimental transmission of the common cold to anthropoid apes and human beings by means of a filtrable agent Apes had been selected as the experimental animal not only because of the difficulty in securing appropriate human subjects and particularly of effectively quarantining them but also because it had been reported by those familiar with the care of the higher apes that these animals readily caught colds from humans These colds were stated to be clinically very similar to those seen in man particularly in children The authors confirmed this opinion by the observation of colds occurring among the apes in the stock room after exposure to workers suffering from colds even though masks were worn All animals were kept during the experimental period in a room maintained at constant temperature and under the most exacting isolation precautions The transmission experiments were performed by the use of Berkefeld filtrates made from nasal washings of subjects with colds injected into the nostrils of the apes Of 16 animals so treated 7 44 per cent contracted colds of which one was atypical In the positive experiments the first symptoms appeared within 36 to 48 hours after the inoculations At this time nasal cultures showed the pneumococcus as suddenly becoming the predominant organism with a marked increase in the numbers of Pfeiffer s bacillus and occasionally of hemolytic streptococci Control experiments had been started using intranasal inoculations of plain broth or heated filtrates These were abandoned in favor of Berkefeld filtrates of nasal washings from the noses of normal subjects taken in the summer months colds being at a minimum and the subjects not having had colds or sequelæ for 3 or 4 months Of 8 control animals so treated none developed colds nor was there any change in the health of the animals moreover there was no change in the bacterial flora of the noses and throats of these control animals

The same experiments were repeated on human volunteers employing the same quarantine and isolation precautions Of 9 men so treated 4 44 per cent contracted colds Only slight changes in the bacterial flora of the nose were found in those humans that developed colds experimentally induced in contrast to the findings in the ape

Almost simultaneously Long Doull Bourn and McComb[38] had carried out a similar series of experiments *using as volunteers healthy young women* The isolation technique and inoculation procedures were similar to those already mentioned Twenty inoculations were performed on 19 subjects with 11 upper respiratory infections resulting 55 per cent In one instance the infective material was transferred from a patient with a cold to an experimental subject and then from subject to subject as each developed a cold until 4 subjects had developed the infection by serial transfer from the original patient

Dochez and his co workers[39, 40, 41, 4] have reported the cultivation of the virus in vitro The culture method is that developed by Maitland and Maitland and by Li and Rivers The culture medium consists of hashed 10 day chick embryos suspended in Tyrode s solution Seitz filtrates of nasopharyngeal washings from an individual with a cold are inoculated into this medium Anaerobic technique must be used since aerobic cultivation results either in a failure of the virus to grow or loss of virulence in a few generations Transfer to new media is made every 4 to 9 days but preferably at 2 to 3 day intervals if a high degree of infectivity and virulence is to be maintained Cultures have been maintained for as many as 144 generations a period of 343 days during which time colds could be produced in a high percentage of volunteers by the inoculation of culture material It has been estimated that by the 15th generation there is a dilution of 1 to 2 quadrillions of the original nasal washings Thirty one controls have been run using uninoculated culture medium or virus cultures inactivated by various means In 23 instances there was no effect whatsoever in 8 there was evidence of minor nasal irritation which always disappeared after the first day More recently[4] the virus has been grown in the chorio allantoic membrane of chick embryo a new departure in the cultivation of viruses

Powell and Clowes[43] using the method of Dochez have cultured the virus for 27 generations a period of seven months At intervals over this period some of the culture material was inoculated into human volunteers in the usual manner Of 32 subjects so treated 22 69 per cent developed colds Among 2 323 control individuals there occurred 203 natural colds $8\frac{3}{4}$ per cent

It is stated that an attempt is being made to prepare a vaccine for prophylactic use though there have been no reports that immune bodies have been found in patients after recovery from the disease such as have been demonstrated following attacks of influenza

It is possible that in the culture media used in inoculation of the nasal passages irritating substances may be present which injure the erectile

tissue and produce local symptoms resembling a common cold and, furthermore the solutions used to suspend inoculation material may act as local irritants The recent discoveries by Stanley and others that large protein molecules, which have the property of propagation in living tissues are responsible for mosaic disease found in tobacco plants raise the question as to whether disease may be caused in human beings by similar agents Apparently tissues may be made immune to these substances That such supposedly inanimate materials might be capable of attacking living tissues and producing disease may be a fact of importance in the study of such diseases as the common cold

As has been stated, previous studies upon the etiology of the common cold have been devoted chiefly to the discovery of some living organism attacking the individual from without Perhaps too much attention has been devoted to this phase of inquiry and too little to the study of the reactions of the host to his environment in particular the reaction of those tissues chiefly concerned in the disease Recently we[44] determined to study the physiological mechanism concerned in the erectile tissue of the nose and selected the common cold as a disease which offered such an opportunity We began by endeavoring to reproduce the common cold For our purpose a room was constructed wherein the temperature and humidity of the air could be controlled accurately The air in the room was kept free from dust and allergens and maintained at a constant temperature of 70° to 71° F dry bulb and 60° to 62° F wet bulb which gives a relative humidity of 55 per cent The air flow was kept at approximately 66 cu ft per minute which affords a cooling power of 6 or 7 or within the normal limits determined by Hill Under these environmental conditions subjects could be kept comfortable throughout the duration of the experiments Groups were chosen of subjects who were known to be susceptible to colds and who had not suffered recently from colds and these were exposed in the room to sufferers from the common cold in its early stage The exposures were as prolonged and as intimate as those which obtain in the ordinary conditions of a household Nineteen subjects were divided into groups of from three to five subjects each and each group was exposed to a person who was in the stage of active secretion and sneezing Two other groups of four subjects each were inoculated with fresh nasal secretions each group receiving directly into the lacrimal sacs material from a different sufferer In addition to inoculation fresh secretions were applied to the thermometers and to the rims of the drinking glass used in common by the subjects In this latter experiment one subject was used as a control Among the 27 subjects of the experiments no symptoms or signs of the common cold

were noted during the period of isolation which was continued for from four to six days

These experiments conducted under constant environmental conditions suggest that the common cold is not as contagious as is generally believed It has not been disproved that under variable environmental conditions bacteria or viruses may not be important etiological agents

Our surprising results led us to give considerable thought to the mechanism of the reacting tissues of the nose As an organ the erectile tissues have well defined functions They vary in size depending on the state of engorgement The amount and character of the secretion changes from time to time The action of the cilia increases or diminishes Throughout these ranges of activity the membranes normally function to warm the air to add moisture to the air when required and to serve as a barrier against inhalation of dust and other extraneous matter

All organs produce characteristic symptoms and signs however obscure when disturbances in function occur The erectile tissue of the nose reacts to injury in certain characteristic ways If the diseases frequently confused with one another and designated as the common cold hay fever vasomotor rhinitis and iodism are all to be considered as reactions of the erectile tissue to injury from without or to disturbances in nervous and vascular control within the body it may be readily understood why there is so much confusion in diagnosis The physical examination of subjects with these reactions shows nothing consistently diagnostic The hay fever patient makes the diagnosis for the physician by recounting previous experiences In recent years studies in the field of allergy have aided in the discovery of susceptibility of persons to allergens and we no longer consider hay fever to be an infectious disease merely because it attacks many persons in one district almost simultaneously Likewise the large groups of people who suffer from sneezing and lacrimation when exposed to dust storms or to irritating gases are not deemed to be infected It is to be hoped that recent studies on influenza will aid in the differentiation of this disease from the common cold Yet if a filtrable virus is found to be one of the causes of a characteristic response in the nasal mucous membranes there may still be other causes due to physical factors in the environment which may produce the same symptoms in a large number of subjects

It is suggested that the common cold may be due to failure of the individual to react properly to physical factors in his environment Among these factors overcooling seems to be prominent The seasonal incidence suggests that some change in weather at the beginning of autumn precipitates an outbreak After the warm summer months the

reactions to external cold are minimal but increase as the weather becomes colder It is a common experience for the onset of the nasal symptoms of a common cold to occur when exercise and excessive perspiration have been followed by chilling Older persons avoid a cooling draft because it precipitates bouts of sneezing and colds In regions of colder *climate the treacherous sunny days of spring long have been avoided by* the weak and tuberculous as has been mentioned often by early writers This springtime outbreak of the common cold may be due to overcooling of the body through contact with cold wet clothing or perhaps to the deceptive warmth of the sun when the ice is melting

The same environmental factors, which affect the body may affect the mucous membrane of the nose through general reactions on the circulatory system and through the local direct action of cold air upon the erectile tissue of the nose If the local circulation is increased in order to make the inspired air warm and moist a state of congestion may result which gives rise to the symptom complex The limited capacity of the veins in the turbinates to carry off the increased blood supply increases the congestion further In the later evolution of the local process following this primary state of congestion sneezing rhinorrhea and obstruction of the nasal passages occur The constitutional symptoms and signs and the response of patients to general treatment directed toward relaxing the peripheral vessels and to local constricting substances support this conception The lack of acquired immunity is strong evidence against any known pathogenic bacterium or virus being the etiological agent

Consequently the etiology of the common cold is chiefly the failure of the individual to make rapid adjustments to environmental changes and is due to the insult of wide temperature fluctuations on the nasal mucous membrane the concomitant effect of overcooling on the body increased by wetness dampness and draught and the exacerbation of these factors in the presence of lowered body resistance chiefly due to fatigue from various causes The proponents of the virus theory may raise their voices in protest and claim that all the above are but incidental factors that better permit invasion of the virus and that with sufficient exposure to the infective agent their presence is not even required Again the burden of proof rests on the exponents of the virus hypothesis The whole disease state as outlined above can be explained without recourse to a living agent as the motivating force On the other hand the experimental work on the virus is far from conclusive The incidence of transmission is low the results in large series reported by some workers are definitely negative the likelihood of irritation from suspension solutions and culture

media are not completely ruled out and the absence of immune bodies and the short period of immunity in a virus disease require explanation We feel therefore that it is more logical to consider the etiology of the common cold as due to environmental change and its related factors rather than to transfer allegiance to the new hypothesis of virus infection The former can be explained adequately by physicopathological mechanisms the latter has still too few facts to prove it or rather too many *loopholes to allow one to believe it*

Symptomatology

One fact that contributes to the confusion about the common cold is that it is a disease which lacks sharp clinical definition This results in the use either of a multiplicity of diagnoses each with its own set of symptoms or of one broad diagnosis to cover many conditions with a list of symptoms so extensive as to permit this diagnosis to cover allied conditions such as mild influenza hay fever pharyngitis bronchitis etc Care must be exercised to limit the number of symptoms on which the diagnosis of the common cold is based

The typical course of an attack of the common cold is as follows The prodromal symptoms are dryness and irritation of the nasal passages and usually also of the nasopharynx which is a continuation of these passages Slight itching may accompany the irritation particularly about the nares and in the nasopharynx together with dryness of the mouth particularly of the hard palate Typically the prodromal symptoms begin during the late afternoon or evening and the patient awakes with them the acute symptoms following within a few hours However the prodromal symptoms *may begin upon awakening in the morning in which case they* last but a few hours at most Sometimes they do not occur at all

The acute symptoms usually begin with or follow shortly after a generalized sensation of coldness or chilliness The term chilliness is a poor one since it may be confused with the chills that are seen in malaria and other febrile states The patient complains of being cold of feeling chilly in that sense only He may shiver but he does not shake which is a simple way of distinguishing between chilliness and chills At this time the oral temperature usually is subnormal Within a few hours or less the peripheral vascular system constricts further and then the patient becomes feverish This feverishness refers to the sensation experienced no actual fever is demonstrated by the temperature curve which remain normal or may rise only a few tenths of a degree Fahrenheit This reaction is to be expected because of the peripheral vascular constrictions

That the symptoms mentioned above probably are not the chills and fever found in acute infections is shown by the fact that the number of micro organisms in the secretions is not increased In fact it has been reported many times that even the saprophytic bacteria normally present either are diminished in number or are entirely absent during this stage No clinical laboratory method has been found to demonstrate whether or not a virus is present

At this time a profuse watery nasal discharge begins accompanied by frequent and occasionally violent sneezing With the feeling of increased warmth the secretion of perspiration diminishes or entirely disappears at the same time the amount of urine excreted increases and becomes of pale color and low specific gravity

The acute stage may follow some already existing affection of the respiratory tract When such occurs the onset of the common cold is sudden and without prodromal symptoms The course is typical and neither condition seems to modify the other except to increase general malaise and other constitutional symptoms Colds may occur during attacks of bronchitis tracheitis pharyngitis and following laryngitis The last mentioned occurs frequently enough so that laryngitis with hoarseness or loss of voice may almost be considered a prodromal state Colds complicate attacks of sinusitis also and frequently occur with or following repeated attacks of hay fever

This acute stage may last from several hours to a day usually not longer and it merges gradually into the healing stage The nasal secretion becomes thicker and finally extremely sticky and tenacious this is due to a change from the thin watery secretion to one more mucoid in type and also to exfoliation of cells The sneezing abates but usually continues to some extent until oral breathing becomes necessary because nasal respiration previously not much disturbed now becomes practically impossible This is due chiefly to the swelling and turgescence of the turbinates which may completely block the air passages and to some extent to the excessive production of mucus which may be blown out only with great difficulty if at all Oral breathing usually adds to pharyngeal irritation and to irritation of the deeper reaches of the respiratory tract The descent of a cold can be explained best on this basis The sense of smell becomes greatly diminished or absent and the taste of food therefore is practically lost Continuous blowing of the nose results in excoriation of the external nares sometimes to an extreme degree of tenderness This irritation is from the handkerchief rather than from action of the secretions Cough from post nasal dripping is a constant symptom which also adds to the pharyngeal irritation Occasionally a laryngitis and

tracheitis are present In some instances the Eustachian tubes are blocked by the turgescence leading to interference with hearing and a sense of fullness in the ears

It is a common experience that when the chilliness subsides and sweating begins the sense of well being returns to the sufferer provided no complications ensue It has been noted likewise that the urine now tends to return to normal but first becomes more highly colored and less abundant The alterations in the urine during the attack illustrate the adjustments in the water balance through changes in the general circulatory system which accompany the local disturbances in the nose The volume and concentration of urine during the attack are such as occur in constriction of the periphery e g from drugs or cooling This is the reverse of the renal circulatory state seen in febrile episodes

The healing stage is that of the longest duration and it is early during this stage that the constitutional symptoms are the most marked These consist of a feeling of general malaise headache usually slight although severe if the sinuses are blocked loss of appetite due chiefly to distaste for tasteless food cough and constipation The general malaise is the most prominent symptom How many of the others are due to complications of the disease rather than to the disease itself it is difficult to state

During this stage the bacterial flora increase considerably in number including the saprophytic bacteria that are normally present and occasionally organisms not common to the individual but spread to him by contact from the local population Pathogenic organisms such as the pneumococcus streptococcus etc are found sometimes Their advent causes the secretions to become purulent to a greater or less degree and may result in serious complications such as pneumonia

Healing which normally would be complete by the fourth to the sixth day often is prevented by the secondary invaders These cause complications to supervene and rare is the individual who escapes them The complications merge their course with that of the precipitating illness to such a degree that the symptomatology of the later stages becomes confused and the duration of illness is prolonged without a break The most frequently complicating diseases are sinusitis and bronchitis although otitis media tonsillitis pneumonia etc are not uncommon Discussion of these will be taken up in a later section

As has been stated already there is no sharply defined clinical picture of the common cold its symptomatology merges with that of allied respiratory conditions Townsend and Sydenstricker[19] in an investigation of the percentage frequency with which symptoms occur in various respiratory conditions obtained interesting results Their tables are compiled

from bi monthly reports on respiratory disease received from members of the faculties of colleges scattered through the United States and from medical officers of the United States Army Navy and Public Health Services Each of the subjects in the survey reported for himself and for his entire household The classification included six diseases so that multiple diagnoses were possible During the year 1924 4 855 attacks of respiratory disease were reported of which a diagnosis of common cold alone was made in 50 73 per cent and common cold in combination with other respiratory diseases except influenza or pneumonia in an additional 24 88 per cent Thus the common cold alone or in combination was found to be responsible for 75 61 per cent of cases of respiratory disease

The percentage of occurrence of certain symptoms in those respiratory attacks for which the only diagnosis reported was cold in the head or nose are shown below for 3 545 cases The frequency of occurrence of these symptoms when other respiratory disease was present has been omitted here

Symptom	*Per Cent*
Inflammation of eyes	12
Running nose	81
Obstruction of nostrils	44
Cough	31
Expectoration	12
Headache	19
Tightness of chest	4 9
Sore throat	14
Sudden onset	37
Chill or chilliness	3 4
Fever	13
Aching in body or limbs	14
Constipation	10

The authors conclude It will be seen from this table that in each of the diagnostic groups (the six which the authors gave their subjects a chance to choose from) *every one of the thirteen symptoms which are listed is included* and that except hay fever the groups are differentiated from each other not by the exhibition of different kinds of symptoms but by different frequency distribution of the same symptoms

Diagnosis

The diagnosis of the common cold would not be difficult except for the fact that the symptomatology is so complex that in certain cases

many allied respiratory affections also may be called a cold Too frequently the physician takes into account the patient s self diagnosis and lets his own diagnosis be colored by if not entirely based on this It has been our experience that otorhinolaryngologists frequently are unable to make a diagnosis by examination alone and without the patient s diagnosis This may not be true in cases of allergic rhinitis in which condition the diagnosis is however based only on the paleness of the mucous membrane

The common cold must be distinguished from (1) hyperemia due to local irritations (2) allied respiratory diseases (3) influenza and (4) infectious diseases in their incipiency

Hyperemia — There are many agents which may produce a greater or less degree of hyperemia of the nasal mucous membranes with sneezing burning of the eyes lacrimation and profuse watery nasal discharge Chief of these are allergens which cause hay fever The seasonal incidence the nature of constitutional symptoms and the results of skin tests aid in the diagnosis of this condition Other factors causing hyperemia are irritation from dust such as is encountered in certain industries in dust storms and in households the action of noxious gases such as chlorine ammonia etc and the effect of drugs such as iodides which produce profuse rhinorrhea in sensitive persons often when given in very small doses and when first administered Sudden inhalation of cold air for short periods of time frequently produces a transient rhinorrhea as anyone can attest who has walked against a cold wind This indicates extreme turgescence of the nasal mucous membrane in an attempt to raise the temperature of this air The rhinorrhea is partly a result of this as well as of a reaction against mechanical trauma resulting in excessive secretion as a protective measure Initial vascular constriction of the entire face as a reaction to cooling and subsequent vascular relaxation probably accompany and are a part of this reaction

(2) *Allied respiratory diseases* to be differentiated include sinusitis In sinusitis the secretion always is purulent and may be found to contain the exciting organism in large numbers Characteristically the secretion is increased by bending the head forward in antrum infections and the pain often intense is localized The condition also is more chronic than the common cold Tonsillitis pharyngitis laryngitis tracheitis bronchitis and otitis media should give no difficulties in differential diagnosis They frequently follow but seldom precede a cold

(3) The differential diagnosis of *influenza* is important because of its epidemiological characteristics and because the treatment is different The distinction may not be easy to make in non epidemic times Influenza

is much more of a constitutional disease than is the common cold and the local symptoms usually are much less marked though occasionally they may be severe In most cases the nasal secretions are of smaller quantity The throat is drier and more irritated Fever occurs early and often is high Prostration is greater and the muscular and osseous pains are characteristic The general malaise is much greater than in the common cold and the disease is more incapacitating convalescence is prolonged A leucopenia usually is found The inoculation of susceptible animals and the development of immune bodies in the serum during convalescence confirm the diagnosis

(4) In certain *infectious diseases* notably measles and in some cases syphilis rhinorrhea occurs as one of the prodromal symptoms or at the onset of the disease

COMPLICATIONS

The common cold is a mild non fatal disease lasting for a short period only and followed by complete cure Complications always due to secondary infection occur very frequently They begin in the later stages of the cold and blend so well with its course that most individuals do not distinguish between the two but state that the cold has settled in the throat or chest The complications are annoying often chronic occasionally serious and may lead to fatal termination more often than has been suspected Fatalities occur more frequently in children in the chronically ill and in the aged

Dochez[46] in reporting on the variation of *Hemophilus influenzæ* (*B influenzæ*) says These observations confirm our previous studies which indicate that one of the most important effects of the virus of the common cold is to incite activity on the part of potentially pathogenic micro organisms present in the nasopharynx at the time of infection Whether this action is directly operative upon the micro organism influenced or is an indirect effect of tissue reaction cannot be stated Whatever the mechanism there is no doubt that the damage to and the lowered resistance of the nasal mucous membrane provides a good opportunity for growth not only of the normal bacterial flora but also of such pathogenic organisms as the streptococcus and the pneumococcus

The complications which occur frequently are involvement of the nasal mucous membrane sinusitis pharyngitis tonsillitis tracheitis and bronchitis occurring less frequently but of more serious import are otitis media and pneumonia

Involvement of the nasal mucous membrane is so common that it

scarcely should be considered a complication The normal bacteria either absent or diminished in number during the stage of acute rhinitis later come into prominence and may multiply greatly The secretion at first thin and watery becomes more mucoid and finally purulent the degree of purulence depending on the number and type of secondary invaders This involvement is of greater consequence than only that of prolonging the course it also provides a locus of infective material which drops into the pharynx especially at night and the infection may spread into the trachea and throughout the bronchial tree Another mechanism which may produce symptoms in the lower respiratory tract or may aid in preparing the field for the secondary invaders is the oral respiration necessitated by blockage of the nasal passages When this occurs cold dry air may strike the pharynx and the bronchial tree and their tissues are not constituted to withstand chilling or drying and are unable to prepare this air for the lungs Thus mechanical irritation leads to hyperemia excessive production of mucus and lowered tissue resistance

Soreness of the throat is common more so if the tonsils are present and if they are chronically infected Frequent colds with consequent tonsillar involvement constitute one of the major reasons for recommending tonsillectomy When the tonsils are absent pharyngitis manifests itself in hyperemia of the pillars fauces and posterior wall edema of the uvula and some degree of lymphatic involvement Occasionally the last mentioned may be so marked that the lymphatic channels ordinarily not visible stand out as glistening semitransparent cords

Bronchitis does not usually occur if the tonsils are present since these bear the brunt of the descending irritation and check its spread In the absence of the tonsils pharyngitis is not common occurring only occasionally by direct extension from the posterior nasal passages but bronchitis increases greatly in incidence Cough is the most prominent symptom at first paroxysmal in occurrence and later chronic The cough is described as tight or loose depending on the ease with which the secretions are raised Usually these are mucopurulent but again their character depends upon the type of invading organism Bronchitis together with sinusitis is the most chronic of the complications the two may persist for weeks long after the inciting infection has resolved Continuous coughing itself may be a cause of protracted hoarseness and irritation of the throat

Sinusitis is the most unpleasant of the complications that occur Block of the ostia of the various sinuses particularly of the antra occurs each time there is prolonged turgescence of the nasal mucous membrane This prevents escape of secretions and encourages growth of organisms so

that in every attack of the common cold there must be some degree of sinus involvement this is of little consequence since the process subsides rapidly once drainage is re established However in those individuals who have chronic inflammation of the mucous membrane of one or more of the sinuses block of normal drainage leads to an acute exacerbation of the chronic state Sinusitis when it supervenes quickly submerges the antecedent state initiates its own train of symptoms and thereby pro longs the course

Otitis media the most common of all ear diseases, is not an unusual complication of the common cold The Eustachian tube forms a di rect connection between the nasopharynx and the middle ear Increased intranasal pressure such as that caused by blowing the nose may force mucopurulent material into the Eustachian tube The local turgescence may block the ostia, preventing drainage and thus otitis media results from ascending infection and acute mastoiditis may follow this Such a train of events occurs much more commonly in children than in adults

Pneumonia is the most serious of the commonly occurring results of a cold It may be due as much to the events which produce the cold fatigue chilling lowered bodily resistance etc as to extension into the pulmonary tract of the original infection There can be no doubt that the common cold when added to the factors mentioned above may be sufficient impetus to start the pneumonic process which otherwise might have been avoided

Prophylaxis

Prophylaxis like diagnosis and symptomatology is dependent upon etiology and in applying prophylactic measures against the common cold the undetermined etiology is again a handicap It is safe to say how ever that isolation should be accepted by sufferers from this condition as much for esthetic reasons as for prevention of the spread of the possible infection The value of the myriad measures suggested might be questioned Also it is one thing to outline precautions and quite another to enforce them This is particularly true of a condition so prevalent among the population at large and usually sufficiently mild as not to be incapacitat ing Hence contact cannot be avoided easily Prophylaxis resolves itself into two main features (1) measures designed to reduce the chance of exposure to the possible infection and (2) measures designed to increase the resistance of the body

Much has been written pro and little 'con on the contact spread of colds The layman speaks of exposure and wet feet chilling overeat

ing and fatigue as causes and then ends up by stating that he caught cold from someone else Droplet infection spread by the sneezing of sufferers is supposedly the main method of transmittal To prevent this it has been suggested that crowded places be avoided during epidemics that sufferers not be kissed that ventilation of crowded buildings be increased that in dormitories institutions etc space between beds be increased particularly during epidemics that sufferers be isolated and that masks be worn It is believed also that colds may be spread by fomites The possibility of infection by food has been mentioned among other things and through the common towel the common drinking cup and other common utensil If the disease were highly contagious naturally the most effective method would be to stop the infection at its source by the prevention of contamination reaching susceptible persons either through the air or fomites This requires instruction of and cooperation by the individual with the cold

To increase resistance of the body many methods have been suggested some of even less value than the measures designed to prevent spread of infection Measures advocated include removal of foci of infection such as tonsils and teeth operations for straightening the septum dietary measures particularly alkalinization and the avoidance of overeating hardening by exposure to cold air by cold showers and by exercise exposure to ultra violet light or to the sun bacterial vaccine therapy the ingestion of vitamins particularly A C and D and more recently the oral administration of vaccines All of these measures seem rational yet certain investigators have shown each to be valueless and some of them even to predispose to colds Nevertheless various of these measures are still advocated and in certain cases still seem to be of benefit It is reasonable to expect that measures to promote normal reactions to cooling and the avoidance of overcooling of the body and of overeating and fatigue may prevent the onset of a cold whether the cause be a virus or a reaction to variation in temperature

Of all the various methods of prophylaxis bacterial vaccine therapy is the best known and most widely used There have been many reports as to its efficacy which have been followed by later reports of a negative nature or denial of its efficacy The use of vaccines began during the time when bacteria were indicted as the specific cause of colds This therapeutic measure persisted after bacteria were admitted not to be the etiologic agent for two reasons (1) Reports as to the use of vaccines were favorable and continued to be so the reason for this now being assigned to a non specific foreign protein reaction (2) Bacteria are known to be secondary invaders and it was presumed that vaccine pre

vented or greatly reduced these complications Recently the use of vaccine by oral administration has come into prominence Advocates of this form of treatment are Thomson[47] and his co workers in England and Rockwell[48 49] and his co workers in this country The principle is that of heterophile antibody production It is stated that since the heterophile antigen prepared from the common secondary invader can be administered orally then frequent administration is practical This becomes necessary when immunization persists but a short time However it remains to be proved that immunity against a common cold or against the secondary invaders can thus be developed

In regard to the possibility of the production of immunity either natural or acquired it is of interest to note the comments of Dochez and his co workers on their preliminary observations on apes Rarely have they been given or have they caught colds in less than three months after having a previous infection and in most cases the interval between infections has been longer This has suggested the possibility that there is a period of insusceptibility or of immunity of 3 or 4 months duration in these animals succeeding colds Yet 3 to 4 months compared to the usual immunity conferred by a disease is infinitesimal particularly when compared to the usual virus disease from which with few exceptions the immunity is of life long duration

Prophylaxis is simply a matter of common sense the application of which many individuals do not consider worth the effort in order to avoid *such a mild condition as a common cold* First and foremost is the avoidance of trauma to the nasal mucous membrane and it is not so much the inhalation of cold air that is inadvisable as it is the sudden change from inhalation of relatively warm dry air to inhalation of air that is cold and moist This change is difficult to avoid during the cold winters in view of the modern type of heating The present heating systems such as furnace steam radiator etc warm the air but add no moisture to it with the result that as the temperature goes up the humidity goes down In consequence the nasal mucous membrane is forced to continue its function in order to add moisture to the air Another result of warm dry air is the requirement for a higher temperature in order to maintain comfortable conditions while at rest This results in a greater variation between indoor and outdoor temperatures than would be necessary with the proper humidification on heating The effect of going out on a cold day then is to chill the body but particularly the nasal mucou membrane when it is in a partly turgid state and this results in definite local physical injury A handkerchief or other piece of cloth held over the nose during the first few minutes of exposure is of value in permitting

the change to be gradual and is indicated for persons particularly susceptible to colds Naturally the sensible precaution would be to provide adequate humidifying apparatus in conjunction with heating systems This would permit the nose to be at rest on sudden exposure to cold air lessening the traumatic effect

Second and of paramount importance is the avoidance of overcooling of the body or of excessive heat loss whether this be due to exercise and then rest in a cold place to cool off to draughts which are worst on the back of the neck and over the ankles in susceptible individuals to the continued wearing of wet shoes and stockings or even wet clothing particularly while at rest when compensatory heat production has ceased or to any other of a number of circumstances

Third and the most difficult to prevent is the decrease in bodily resistance whether from fatigue from intercurrent infections usually of the accessory nasal passages or the lower respiratory tract from improper diet excessive consumption of alcohol or irritation of excessive tobacco smoking from lack of proper exercise lack of conditioning or failure of acclimatization These are individual factors in each patient and some of them must occur unavoidably at some time in everyone

Treatment

The methods of treatment of the common cold are numerous Almost everyone has a favorite formula or procedure and scarcely a sufferer escapes receiving gratuitous advice from his fellows All of the approved medicaments used fall into two categories (1) those which shrink the erectile tissue of the turbinates and (2) those which open the peripheral vessels Frequently a combination of these two types of treatment is employed

Among the agents used in local treatment are such constricting drugs administered in solution as adrenalin ephedrine and related compounds and cocaine which should be used with great caution Hypertonic solutions of salts may exert a beneficial effect locally and soothing or slightly anesthetic preparations may minimize the tendency to sneeze Oily substances may prove harmful They prevent the mucous membrane from performing its natural function of warming and adding moisture to the air and also the oily bases may enter the bronchial tree and cause serious and permanent fibrotic change This danger may be trivial when such drugs are used only for a short period in a transient ailment such as the common cold but the hazard is great when they are used for long continued nasal disturbances The widespread use of petroleum oils

sprayed or dropped into the nostrils of children, any time but especially at night should be abandoned

General treatment consists of a variety of methods to promote vaso dilatation of the peripheral vessels Among the drugs of value are acetylsalicylic acid pilocarpine opium and papaverine Sedatives such as bromides acetphenetidin and many others have been used either in combination with the vasodilators or alone Hot baths and hot drinks have been household remedies for generations and are of value if the sufferer goes to bed immediately and protects himself from chilling afterwards The old rock and rye concoction and the hot toddy still are used extensively and generously to the point of diplopia in many subjects There is now scientific evidence that the peripheral vessels are relaxed by the use of moderate amounts of alcohol and that they may be excessively relaxed by large amounts The dangers of overcooling following the use of alcohol to excess are apparent because of the frequency of occurrence of pneumonia among those exposed to overcooling following an alcoholic bout

Recently Diehl[30] investigated the use of various opium derivatives in the treatment of the common cold The use of Dover s powders is an old method of treatment for which good results had been claimed though their use did not become general and lately has fallen into discard Diehl used not only this but also the various fractions of opium such as dilaudid papaverine codeine etc singly and in combination He also investigated acetylsalicylic acid alone and combined with acetphenetidin and caffeine or with sodium bicarbonate lactose tablets were used in control experiments Of 216 subjects 75 per cent reported definite improvement or complete cure of their colds within from 24 to 48 hours after taking a codeine papaverine mixture The results were a little better with the dilaudid papaverine combination and practically as good with the morphine papaverine mixture Diehl concluded however that for general use a combination of codeine and papaverine seems most desirable because of the high percentage of good results obtained with it its low toxicity and the absence of danger or at least of practical danger of habituation to it

It is interesting to note that with the lactose tablets 35 per cent of 110 subjects reported definite improvement or complete cure of their colds within 24 to 48 hours To quote the comments that were made on the report cards by persons who had received only lactose tablets would serve admirably as testimonials concerning the value of these tablets for the treatment of colds In other words 35 out of every 100 individuals receiving any form of medication for an acute

cold will be greatly benefited Thus the apparent cure of 75 per cent by the codeine papaverine or other opium derivative mixture actually is due to the drug used in only about 40 per cent of cases One wonders therefore if the use of opium derivatives is warranted even though they be practically free of danger of producing habituation

Many public health authorities advise sufferers to rest in bed throughout attacks of the common cold presumably to prevent spreading the supposed infection to others and perhaps also to prevent exposure of inflamed mucous membranes to more dangerous organisms Subjects usually are more comfortable if they are resting in a warm bed fortified with warm drinks with the customary supply of wipers available for the nose The use of soft absorbent paper wipers is more esthetic and probably less irritating to the skin than frequent rubbing with dampened handkerchiefs

A warm room with a relatively high humidity reduces the nasal symptoms remarkably and probably prevents many of the complications in the throat and lower re piratory passages A steaming kettle of water near the patient s bed may be helpful if the air in the room cannot be kept warm and moist but this is a crude method of providing a constant and beneficial atmosphere for the inflamed respiratory tract It is customary to add aromatic oils for their psychotherapeutic rather than medicinal value The entire body benefits from the warmth of the room which aids in dilating the peripheral vessels

Discussion of the treatment of complications is beyond the scope of the present paper Such complications may arise as the result of injury to the mucous membrane from the external nares to the alveoli Unprepared air may be as injurious to the lower respiratory passages as is some noxious gas or dust which has not been removed by the natural defenses in the nose

Complications arise also from obstruction of the ostia of the ducts leading from the sinuses or ears in which case they may be dealt with according to rational principles If the nasal membranes on the turbinates can be restored to a more normal state the sinuses can drain adequately If deviations of the septum or abnormalities in structure of the turbinates exist these can be corrected insuring the subject from such complications in subsequent attacks Happily the custom of snipping bits from the turbinates which was practiced widely in former years is passing Removal of large and disea ed tonsils and of adenoids may be beneficial in increasing the diameter of the respiratory channel in preventing pharyngeal complications and in removing loci from which secondary infection can spread

In summary no single outline of treatment can be prepared which will fit each individual case first because there is no specific therapy and second because the symptoms most requiring alleviation are almost always due to the secondary infection in which the time of occurrence and the clinical pattern presented vary so greatly As a general rule every patient with a cold should be required to go to bed for the first twenty four or even better for the first forty eight hours The diet should be soft or even liquid at first with the carbohydrates and starches reduced in amount Third intake of fluids should be pushed to 4000 to 6000 c c whether of water fruit juice milk tea coffee etc is immaterial The old adage stuff a cold and starve a fever happens to be incorrect in both respects it should be reversed for colds and prolonged wasting fevers Unfortunately it still persists in lay usage in the way quoted in the previous line

The art of medicine enters into the treatment of a cold perhaps more than into any other phase of medicine The best treatment is not accomplished by laying down an arbitrary plan of procedure including certain drugs in certain dosages but is attained by discovering how the patient usually treats his colds then modifying and amplifying this The goal to be strived for is to have the patient at rest and warm to keep his periphery open but his nasal mucous membrane shrunken and to promote elimination through the skin kidneys and bowel To get the patient to rest is difficult too often treatment has to be limited to that which is possible while the patient is not only ambulatory but is carrying on his usual occupation

The periphery may be opened by keeping the patient in bed in a warm room with plenty of bed clothes the judicious use of alcohol in a hot drink before going to sleep acetylsalicylic acid grs x (0 65 gm) every four hours while awake a hot mustard foot bath twice a day hot drink usually unsweetened lemon juice two or three times a day The nasal mucous membrane may be kept shrunken by the use of ephedrine solution one to three per cent instilling three to five drops into each nostril as often as required Where nasal turgescence is marked capsules containing ephedrine sulphate grs 3/8 (0 025 gm) and amytal grs 3/4 (0 05 gm) given twice daily usually is sufficient to produce the desired effect amytal greatly reduces the unpleasant systemic effects of the ephedrine The peripheral effects of ephedrine by mouth may be offset in part by the several methods of provoking vascular dilatation suggested above Elimination by bowel may be promoted by a variety of means either cascara sagrada or the milder saline laxatives being the best laxatives for this purpose

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CHAPTER XXXII

TULAREMIA

By EDWARD FRANCIS

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Definition—Tularemia is an infectious disease caused by *Bacterium tularense*, found in nature as a fatal bacteremia of rodents, especially wild rabbits, and transmissible to man by the bite of an infected blood sucking fly or tick or by the lodgment on his hands or in his conjunctival sac of portions of the internal organs or body fluids of infected animals or ticks The disease is named, tularemia, on account of the presence in the blood of the causative organism, *Bacterium tularense* This organism was so named by McCoy and Chapin[38 39] who discovered it in 1912 as the cause of a fatal epidemic among the ground squirrels in Tulare County, California Tulare County was so named because that region was once covered with extensive marshy beds of the reed tule, a large variety of bulrush

History

McCoy[3] in 1911 discovered the disease in the California ground squirrel and named it "a plague-like disease of rodents McCoy and Chapin[38 39] in 1912 discovered the causative organism and named it *Bacterium tularense* McCoy and Chapin in 191 reported complement fixation and agglutination of *Bacterium tularense* by two human serums in their laboratory Pearse[46] in 1911 described six cases clinically occurring in Utah Martin in correspondence in 1907 undoubtedly called attention to cases in Arizona, one of which in 19 5 still showed agglutinins for *Bacterium tularense* in his blood Wherry and Lamb[56] in 1914 first isolated *Bacterium tularense* from a human case occurring in the ophthalmic practice of Vail and isolated the same organism from two rabbits found dead in nature Francis[8] in 1919 and 1920 recognized the bacteriologic identity of the human disease popularly known in Utah as deer fly fever' and the "plague-like disease of rodents" occurring in California and named the disease tularemia[9 18 19]

Tularemia is an outstanding example of a disease first described unimpeachably as to its bacteriological cause and its pathological manifestations *in a naturally infected wild animal and soon thereafter* recognized as having world distribution as a disease of man The rule usually has been the reverse first description as a human pestilence and later described as to bacteriological zoologic or insect source

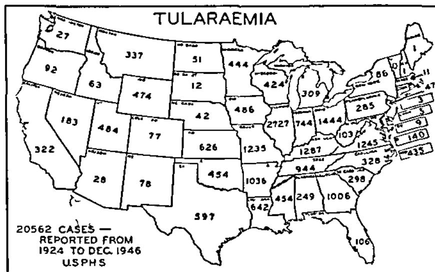


Fig 1—This shows the distribution of 20562 reported cases of Tularemia in the various states of the United States

Zoologic Distribution

Bacterium tularense is wide spread in nature[61] as a bacteremia of wild animals which accounts for its ready spread from animal to animal or from animal to man by blood sucking insects—lice flies ticks or fleas Under a subsequent title in this chapter Sources of human infection *one finds an enumeration of 30 animals and insects which have conveyed* the infection to man And under the title Potential sources of human infection are listed 13 animals and ticks and fleas found infected in Nature in the United States these are therefore only potential sources

Definition—Tularemia is an infectious disease caused by *Bacterium tularense*, found in nature as a fatal bacteremia of rodents especially wild rabbits, and transmissible to man by the bite of an infected blood sucking fly or tick or by the lodgment on his hands or in his conjunctival sac of portions of the internal organs or body fluids of infected animals or ticks The disease is named, tularemia on account of the presence in the blood of the causative organism *Bacterium tularense* This organism was so named by McCoy and Chapin[3, 39] who discovered it in 1912 as the cause of a fatal epidemic among the ground squirrels in Tulare County California Tulare County was so named because that region was once covered with extensive marshy beds of the reed tule a large variety of bulrush

History

McCoy[37] in 1911 discovered the disease in the California ground squirrel and named it a plague-like disease of rodents McCoy and Chapin[38, 39] in 1912 discovered the causative organism and named it *Bacterium tularense* McCoy and Chapin in 1912 reported complement fixation and agglutination of *Bacterium tularense* by two human serums in their laboratory Pearse[46] in 1911 described six cases clinically occurring in Utah Martin in correspondence in 1907 undoubtedly called attention to cases in Arizona one of which in 19 still showed agglutinins for *Bacterium tularense* in his blood Wherry and Lamb[56] in 1914 first isolated *Bacterium tularense* from a human case occurring in the ophthalmic practice of Vail and isolated the same organism from two rabbits found dead in nature Francis[5] in 1919 and 1920 recognized the bacteriologic identity of the human disease popularly known in Utah as deer fly fever and the 'plague like disease of rodents occurring in California and named the disease tularemia[9, 15, 19]

(4) Tick (*Dermacentor andersoni*)[74] March April May and June are the months recorded for the onset of 53 cases due to this tick These months correspond to the season of greatest activity of this tick in Montana and surrounding states

(5) Tick bite *Dermacentor variabilis* January to October are the months recorded for the onset of 55 cases of tularemia due to the dog tick, *Dermacentor variabilis* which is distributed widely throughout the Southern States and feeds on dogs, rabbits and man

(6) Tick bite *Amblyomma americanum*[1] An epidemic of tularemia occurred among soldiers bivouacked in Tennessee March to December 194, Thirty two of 50 cases gave history of tick bite before onset of symptoms Indentification of ticks collected by flagging in the area showed all specimens were *Amblyomma americanum* the lone star tic *B tularense* was not demonstrated in the ticks

Causative Organism

Bacterium tularense the cause of the disease is a small pleomorphic organism occurring in bacillary and coccoidal forms both in tissues and in cultures a bipolar form occurs in certain cultures The organism is gram negative non motile and non spore bearing it grows only under aerobic conditions its optimum pH range is between 6 8 and 7 3 It ferments[89] glucose levulose glycerol maltose and mannose forming acid but no gas it grows well on coagulated egg yolk and on blood glucose-cystine agar[81] but not on plain agar or in liquid medium without special enrichment Additional efficient media are serum glucose agar glucose blood agar and blood agar each having been enriched by rubbing over its surface a piece of fresh sterile rabbit spleen which is allowed to remain on the medium In cover glass preparations from tissues and cultures the organism stains with ordinary dyes but preferably with crystal violet or Wayson s plague stain In sections of tissues it stains well with azure eosin or with Giemsa s solution preferably the latter The filtrability of the organism has been sudied by Foshay and Hesselbrock[6]

The extraordinary morphology of *Bacterium tularense* and its modes of reproduction has suggested to Hesselbrock and Foshay[96] that the organism should not be included in the genus *Pasteurella* Several investigators[114,11 1*] have demonstrated growth of *B tularense* in liquid medium Several others have demonstrated growth of the organism in the yolk sac of the developing chick embryo[112,113] The organism sur

of human infection because up to the present time transfer of *B tularense* from them to man has not been reported

Geographic Distribution

Human cases have been recognized in 47 states of the United States and in the District of Columbia (Fig 1) The only state in which cases have not been recognized is Vermont

The disease was reported in Japan in 1925, Russia 1928, Norway, 1929, Canada 1930, Sweden 1931, Austria 1935, Czechoslovakia, 1936, Turkey 1936, Italy, one hare 1931, Central Germany, one hare, 1939 Mexico, one questionable human case 1944, Tunisia, one rabbit, 1934, Alaska, in rabbit ticks, 1937 and one human from skinning muskrats 1946, Poland, Warthe river, 194-

Seasonal Incidence[5 84]

Relaxation of the game laws is seasonal and ticks and flies have a seasonal prevalence all of which contributes to the seasonal incidence of human cases All months of the year have witnessed cases contracted in nature Laboratory cases in man are without seasonal incidence, it being "open season" for them all the year around

(1) East of the Mississippi River the months of November, December and January generally embrace the 'open season', during which wild cottontail rabbits are unprotected by the game laws and are hunted and offered for sale in large numbers in the markets Consequently the great majority of human infections east of the Mississippi River have occurred in the months enumerated although, due to lack of such game laws or lack of enforcement, human cases also have occurred in June

(2) West of the Mississippi River jack rabbits are not often eaten they are a pest, and their destruction is often rewarded by a bounty Human cases due to manipulation of the internal organs of jack rabbits have occurred in April, May, June, July August September and October months entirely different from those enumerated for cases east of the Mississippi River

(3) Flies (*Chrysops discalis*)[79] June, July and August are the months recorded for the onset of 68 cases due to fly bites in Utah and surrounding states I believe that cases have occurred also in September These months correspond to the season of greatest prevalence of this fly

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vived five years or longer at a temperature of $-76°$ Centigrade maintained by dry ice, the cultures being on blood glucose-cystine agar in glass test tubes stoppered with paraffined cork stoppers and closed with metal screw tops and unopened for five years until September 3 1947 On the latter date there was no evidence of drying of the water of condensation, of softening of the culture medium or of diminution of

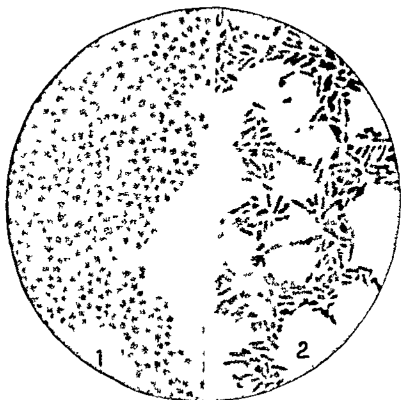


Fig —Bacterium tularense before (1) and after (2) a single transfer to fresh culture medium Note transformation from coccoidal form to bacillary form (*Francis Army Institute of Pathology No 57 03A*)

virulence from the original maximum virulence A culture survived four years or longer after transfer to small glass ampules then frozen dried in vacuum sealed in a flame and stored at room temperature until April 1946[167]

Pathology[73 74 104 10]

Only the outstanding pathological changes due to an acute infection will be stated briefly as they appear in (1) guinea pigs and rabbits (2) white mice and (3) man

(1) Guinea pigs and rabbits may be inoculated by rubbing a culture or a piece of infected tissue on the clipped abraded skin of the abdomen or by subcutaneous or intraperitoneal inoculation Death will occur between the fourth and sixth days when using a virus of maximum virulence

The superficial lymph nodes, draining the site of inoculation and the deep nodes to which the superficial nodes are tributary are enlarged and pale and the surrounding tissue is injected and edematous The nodes are the seat of a dry granular caseation and they shell out readily from their capsules in a firm mass

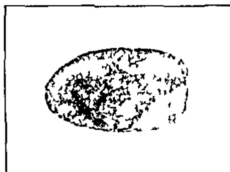


FIG 3.—Tularemia in spleen of guinea pig Note arears of focal necrosis *(Photograph from collection of Army Institute of Pathology)*

The spleen especially and the liver are enlarged Studded over the surface are globular white nodules ranging from a size which is barely visible even in direct sunlight or strong electric light, to 1 mm in diameter (Figs 3 and 4) The nodules are not raised but are submerged coming just to the surface where they appear as circular Cut section of the spleen shows these nodules to be globular and closely packed throughout the pulp resembling bunches of grapes If the pulp is dragged back and forth over a piece of paper the individual nodules of all sizes can be teased apart and rolled out under the pressure of a dissecting needle as if each had an organized wall

The lungs of a guinea pig dying of an acute infection seldom show visible lesions but rabbit lungs quite commonly are studded over with the small circular pale nodules which are so characteristic of the spleen

Microscopic section of spleen liver and lymph nodes show numerous circular small areas of focal necrosis at the center of which are masses of fragmented nuclei but microorganisms are almost entirely absent

Cover glass preparations of fresh spleen, liver, lymph nodes and blood show a great scarcity of microorganisms It should not be unexpected to find none

(2) White mice die in from 3 to 4 days The lymph nodes are barely discernible never showing the enlarged caseous appearance seen in guinea pigs and rabbits The liver appears quite normal on gross inspection The spleen is studded over with circular, white, small nodules

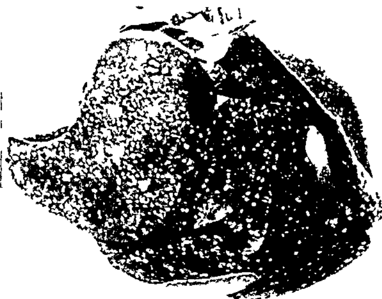


Fig 4—Tularemia Spotted liver of rabbit showing areas of focal necrosis Army Medical Museum No 375 6

as in the rabbit and guinea pig Microscopic sections of the spleen show the same areas of focal necrosis which are seen in guinea pigs and rabbits but microorganisms are numerous The liver shows a most remarkable condition The hepatic cells in great numbers are invaded with microorganisms, which ultimately destroy all trace of the cell nucleus leaving the swollen outline of the cell packed with organisms Normal hepatic cells are seen everywhere adjacent to and between the invaded cells Under the 16 mm objective the invaded cells stand out in blue outline furnishing a striking picture Circular areas of focal necrosis are absent In cover glass preparations of fresh spleen liver and blood microorganisms as a rule, are seen in great numbers

(5) In man acute and subacute lesions are noted

Acute Lesions Within the first two weeks the primary ulcer lymph nodes spleen liver and lungs show focal necroses with nuclear fragmentation and infiltration with polymorphonuclear and large mononuclear cells Some cases have a lobular pneumonia in which monocytes form a prominent part of the exudate and tend to undergo necrosis One can never be sure of staining *Bacterium tularense* in human tissues because of the scarcity of the organisms

Subacute Lesions In microscopic sections areas of focal necrosis are seen which show a central necrotic zone surrounded by a layer of epithelioid cells and fibroblasts in radial arrangement and a peripheral zone of lymphocytes among which are a few giant cells

Sources of Human Infection[7, 81]

Wild rabbits and *hares,* shot and dressed bought or sold in markets skinned or cut up have caused over 90 per cent of cases in the United States *fly* bite (*chrysops discalis*) 68 cases *tick* bite (*Dermacentor andersoni*) 53 cases in Montana and surrounding states *tick* bite (*Dermacentor variabilis*) 73 cases principally in southern states *tick* bite (*Amblyomma americanum*) an epidemic of tularemia among soldiers bivouacked in Tennessee, March to December 1943 *Laboratory animals, autopsied* or *contacted,* 41 cases in the United States and 9 cases in foreign countries *beaver,* skinning 1 case in Wyoming *cat* bites 11 scratches *coyote* bite 1 skinning 2, *dressing chickens* fed with rabbit meat 1 *dog* bite 1 picking ticks from dog 4 *deer* skinning and dressing 1 case in New York *fox,* skinning a red fox and several small rodents 1 case in Maine dressing *fish* baited with rabbit meat 2 *ground hog* skinning 2 *hog* bite 1 autopsy 1 puncture by splintered bone 2 *hawk* after feeding on dead rabbit pecked a finger and caused 1 case *ingestion* of insufficiently cooked *wild rabbit meat* caused 20 cases in 5 families of whom 1 patients died *muskrat* skinning bite 1 *opossum* bite . skinning 5 *pheasant* dressing 1 case *quail* dressing 7 *raccoon* bite . *sage hen,* dressing 1 *bull snake* skinning 1 *sheep contact* and thereby contact with wood ticks and their feces in shearing herding and butchering in the Northwest 12 cases *skunk* bite 1 skinning 5 *ground squirrel* bite in Montana 1 and playing with ground squirrels in Nevada 8 *tree squirrel* skinning 14 bite 1 chewing 1 *weasel* bite *water rats, Arvicola amphibius,* caused an explosive outbreak of about

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thema multiforme and erythema nodosum have been the designations of the lesions observed by several physicians

Leucocytosis —The white cell count is moderately increased and may reach 16,000 but this is not of diagnostic value

Convalescence —Convalescence is slow it is rare for a patient to be at work again at the end of a month, usually the second month is spent lying about the house owing to weakness on exertion and during the

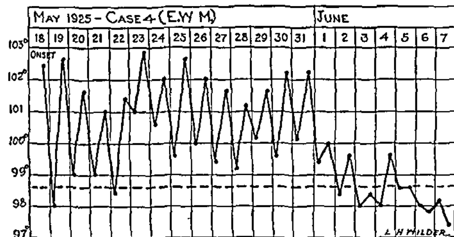


Fig 5 —Temperature curve in a case of tularemia (*Laboratory infection*)

third month only half time work is performed Some have not entirely returned to normal for six months or even a year

Fever —Fever is always present in cases of tularemia (Fig 5) Complete temperature records are available only for the laboratory cases and of these charts there are eleven Viewing the eleven charts one is struck at a glance by the constancy of the sequence of initial rise remission and secondary rise Following the initial fever which lasts one two or three days there is a remission of temperature for one two or three days this is followed by a secondary rise to the original height after which there is a gradual decline to normal the whole febrile period lasting from two to three weeks

The early remission of temperature is accompanied by an amelioration of symptoms, which reflects itself in the conduct of the patient by his leaving the hospital for his home or by returning to work and which reflects itself in the physician's mind by the opinion that the case is

1 000 cases in Russia in 1928 in persons who skinned the rats for their pelts not knowing of that reservoir of infection, a *water-borne* epidemic of 43 cases was reported in 1935 from Russia in peasants who drank from a brook which was thought to have been contaminated by water rats because *Bact tularense* was recovered from the water

Potential Sources of Human Infection in the United States—Animals and insects in the United States from which *Bact tularense* has been isolated in nature but which have not yet caused human cases are as follows California ground squirrels, gray foxes of Minnesota, wild rats of Los Angeles field mice of California and Montana ground squirrels of Utah ruffed grouse and sharp-tailed grouse in Minnesota prairie dog in Utah the tick *Dermacentor occidentalis* in California, the tick *Ixodes ricinus californicus*, fleas off rabbits and hares in Minnesota and off prairie dogs in Wyoming, and fleas and ticks off ground squirrels in Washington Water from ponds and streams inhabited by beaver in Montana has yielded *Bact tularense*

Potential Sources of Human Infection in Foreign Countries—One wild hare at Nurnberg, Germany, 1939 one wild hare in Italy, 1931, lemming of Sweden 1938 one rabbit in Tunisia 1934

Rabbits raised under domestic conditions in rabbitries and hutches although highly susceptible have not been found naturally infected, due probably to their freedom from ticks

General Symptoms and Course[6, 7, 8, 38, 115]

Incubation—The period of incubation may range from 1 to 10 days but in the great majority of cases it does not exceed 5 days the average being about 3 days The *onset* is sudden often occurring while the patient is at work and is manifested characteristically by headache vomiting chills aching bodily pains sweating weakness and fever Loss of weight and prostration are noted during the active state of the disease which lasts from – to 3 weeks Some cases are ambulant throughout

Skin Eruption—A very definite skin eruption usually bilateral was noted in 45 cases It was macular papular pustular, maculopapular papulopustular blotchy or a rash In some instances it was painful and inflammatory but usually it was painless and did not itch Desquamation and pigmented remains have been noted Many acne lesions developed on the back of the thorax during the illness in 2 cases Extreme herpes of the lips was noted in 1 case Jaundice was observed in 1 case Lrv

Relapses—Relapses of fever lasting 6 and 8 days occurred in two laboratory cases after 10 and 8 months respectively Recurring mild attacks of fever have been noted

Sequelae—Recovery usually occurs without evident sequelae

Complications and Death—Recovery without complications is the rule Of 109 cases manifesting pulmonary complications in the pre streptomycin days 51 died 40 within the first month 8 in the second month and 1 in the ninth month thus showing a mortality of 46 7 per



Fig 7—Tularemia ulcer of index finger 18 days after onset from dressing wild rabbits Mr C O R Dr T Cajigas Washington D C Army Medical Museum No 63173 74

cent in tularemic pneumonia according to Francis[87] Of the 51 deaths 30 presented the signs of bronchopneumonia 13 lobar pneumonia 1 interstitial pneumonia 3 showed discrete multiple nodules in the lungs and 1 multiple pulmonary infarctions Of 58 patients who recovered from pulmonary complications 19 required aspiration of pleural fluid at periods ranging from 2 weeks to 5½ months From the chest fluid of 4 patients *Bacterium tularense* was isolated during life 3 to 5 months



Fig 6—Ulceroglandular type of tularemia Crater like ulcer on cheek and enlarged cervical lymph node Photograph taken fourteen days after the onset of illness *(Courtesy of Drs W L and C P Brown El Paso Texas)*

merely one of some ephemeral fever This is particularly true of the cases of laboratory infection without primary lesion and without lymph node enlargements and more especially if the patient is himself a physician

penis one inch from the base A sheep herder in Montana instead of toilet paper, used wool picked from the brush and contracted an ulcer of the anus presumably from tick feces in the wool

Fly bite occurs on the uncovered portions of the head resulting in an ulcer on the temple, cheek, ear, neck, in the hairline or on the back



Fig 8—Tularemia 43709 Ulcer of thumb and axillary bubo after dressing rabbits 40 days after onset (Brown and Hunter)

in the absence of a shirt *Tick bite*[1] is located beneath the clothing or in the hair and has resulted in an ulcer in one of the following locations scalp (occipital) shoulder chest axilla clavicle scapula, deltoid insertion wrist cubital crease, over crest of ilium umbilicus scrotum penis perineum over coccyx buttock, gluteal fold thigh popliteal space knee leg or ankle

Subcutaneous nodules simulating sporotrichosis were noted on the forearm and arm in 7, cases They were distributed not only along the vessels on the anterior surface but also over the posterior surface of the forearm or arm and extended from the ulcer on the fingers to the enlarged axillary nodes The nodules were firm and movable but most of them ultimately suppurated They varied in size from that of a pea to 1 cm in diameter and in number they varied from to 30 They may

after onset. Suppuration of lymph nodes occurred at all periods from 1 to 24 months after onset. Meningeal[119] localization usually is fatal. Death resulted in 12 of 20 ingestion cases.

General peritonitis with plastic exudate terminated 1 case on the twenty-ninth day. A death on the eighth day was preceded by acute diarrhea. Ascitic fluid in 2 cases required tapping 3 and 5 months after onset, the fluid yielding *B. tularense* in both cases. Appendicitis necessitating operation complicated 1 case on the fourth day. Acute pericarditis and femoral thrombophlebitis have been noted. Extensive skin ulcerations in Blackford's case yielded *B. tularense* 5 months after onset. Of 20,562 cases of tularemia in the United States from 1924 to December 1946 there were 1,532 deaths or a mortality of 7.4 per cent.

Clinical Types

Seven clinical types or forms are recognized.

(1) *Ulceroglandular Type.*—An ulcer of the skin at the site of infection followed by a bubo of the lymph nodes, which drain that site, is the typical picture of this type (Figs. 6, 7, 8, 9). Skinning and dressing wild rabbits and hares and other wild animals with bare hands by hunters, market men and others are the cause of over 90 per cent of cases of this type, but tick bite and fly bite cause many cases. The site of infection passes through the stages of redness, swelling, necrosis, suppuration, liberation of a core, ulcer and scar. The ulcer usually is about ⅜ths of an inch in diameter and has a punched out appearance. The primary ulcer usually is single, but occasionally there may be 2 or 3 if the injury is at more than one point. Only the superficial lymph nodes, which drain the ulcer, become involved and not those of the opposite side of the body, unless the primary lesions happen to be bilateral. Redness or red streaks may extend from the ulcer to the lymph nodes. About half of the bubos proceed to suppuration by about the end of a month, while the other half gradually resolve without suppuration.

In addition to the usual epitrochlear and axillary sites of enlarged nodes they may be located over the biceps, midway between elbow and shoulder, brachial, post-axillary, subscapular, subpectoral, pectoral, supraclavicular or subclavicular. Unusual location of the primary lesion on the penis occurred in a man in California who, after killing and cleaning a rabbit, failed to wash his hands before going to the toilet; two chancre-like ulcers resulted, one on the prepuce and the other on the

be purplish and painful Less frequently they appear on the chest back face or legs

(2) *Oculoglandular Type*[90 122] —The primary lesion is a conjunctivitis and is accompanied by enlargement of the regional lymph nodes A study of 78 cases in the United States by Francis yields the following facts The infection was transferred to the eye by the hands while skinning rabbits or crushing ticks or flies between the fingers Spurting of rabbit blood or groundhog bile into the eyes was responsible for 3 infections The patients manifested the general constitutional symptoms of the disease but with primary localization in the conjunctival sac only 3 ocular cases showed simultaneous lesions on the hands The left eye was affected in 41 cases the right in 29 and both eyes were affected in 4 Some of the corresponding regional lymph nodes were always enlarged preauricular, parotid, submaxillary or anterior cervical and in half of the cases they suppurated There are pain photophobia lacrimation swollen lids and conjunctivitis Yellow papules on the palpebral conjunctiva break down into shallow ulcers Unusual manifestations have been steamy cornea once corneal ulcers five times chalazion once purulent dacryocystitis five times, optic atrophy twice rupture of the globe and enucleation once There was no involvement of the sinuses Recovery without sequela is the rule Double optic atrophy resulted in total blindness in one case There were 7 deaths

(3) *Glandular Type* —Infection may penetrate the skin without causing a local lesion but causing enlargement of the regional lymph nodes This type occurred in 24 patients who had dressed wild rabbits in 1 (an experimental human subject) whose hand was rubbed with an infected rabbit heart and in 1 who was tick bitten

(4) *Typhoid Type* —In this type the infection penetrates the skin without causing a primary lesion or regional lymph node enlargement but instead gives rise to a general systemic infection in which fever and prostration are the outstanding symptoms Severe pulmonary or intestinal symptoms have resulted fatally in 10 cases Fifty six laboratory infections in man were of this type and occurred in persons who performed necropsies on infected guinea pigs rabbits or white mice Tick bites were responsible for 3 cases handling of sheep 3 cases skinning of opossum or coyote 2 cases dressing wild rabbits 25 cases and playing with ground squirrels 6 cases

(5) *Meningeal Form*[119] —Of 6 patients presenting the ulceroglandular type of symptoms 5 developed meningitis and died a sixth case died of leptomeningitis



Fig 9 —Tularemia 43545 Ulcer of knee following bite of wood tick, enlarged inguinal glands 70 days after onset (Magath and Yater)

and clerical personnel who only pass through the infected animal rooms even in great numbers have not contracted tularemia by inhalation.

There is no record of a tularemic pneumonic patient infecting a physician, nurse or bedside attendant by inhalation or otherwise, even when the patient's sputum was proven by guinea pig or mouse inoculation to contain *B. tularense*. The sputum of one such patient yielded *B. tularense* on the 1[illegible]th day of illness, of another on the 15th day, of another in daily specimens from the 1[illegible]th day to the [illegible]4th day of illness, of another in daily specimens from the 26th to the 38th day of illness, and of three other pneumonia patients on the 30th, 40th and 49th day of illness respectively. In distinction from plague pneumonia the sputum in tularemic pneumonia is noted for its scarcity of *B. tularense*, which can never be identified with certainty in stained smears of a patient's sputum.

An extreme example of acceptance of the aerial route of entrance of *B. tularense* is the following statement by the Russian epidemiologist Volfertz[1] (his page 190): According to our observation it appears to be evident that persons working in gauze masks are not made sick of tularemia, even when simultaneously working without gloves.

IMMUNITY, SUSCEPTIBILITY AND TRANSMISSION

Noncontagiousness.—No instance has been reported of the spread of the infection from man to man by mere contact.

Immunity[93].—In man one attack of tularemia confers permanent immunity. If by chance such an immune is exposed to reinfection through lodgment of a virulent culture in a wound or crack on his hands, he may contract a local reinfection, but his immunity holds the infection down to a local lesion, the contents of which are harmless to his resistant body but deadly in 5 days to a guinea pig into which it is injected. Such a local reinfection in a tularemia immune individual is designated as an immune reaction, as in revaccination with vaccine virus against smallpox.

Susceptibility.—Degrees of susceptibility are noted as follows: (1) High susceptibility is present in man, monkey, ground squirrel, rabbit, guinea pig, mouse, woodchuck, oppossum, beaver, muskrat, prairie dog and tree squirrel. Guinea pigs, rabbits and white mice have exhibited no evidence of immunity in our laboratory. (2) Slight susceptibility is present in rat, cat, quail, sheep and goat. (3) Nonsusceptibility is found in horse, cow, hog, dog, pigeon and chicken.

(6) *Oropharyngeal, Anginose and Ingestion Forms*—Ingestion of insufficiently cooked wild rabbit meat caused 20 cases in 5 outbreaks in families There were vomiting, pain in the stomach, diarrhea fever enlargement of submaxillary and anterior cervical lymph nodes and in some cases, conjunctivitis Young children, after staggering around developed convulsions, became stuperous and usually died in the first week Adults have died in the second week Other cases have manifested abscesses in the roof of the mouth ulcer on lip, ulcer on tonsil ulcer on posterior pharyngeal wall, ulcer beneath the lower dental plate or ulcers in the pharynx and nasopharynx A water-borne epidemic in Russia caused 43 cases with pharyngeal angina tonsillitis, conjunctivitis and enlargement of regional lymph nodes but no deaths

(7) *Pulmonary Type*—Lobar pneumonia, bronchopneumonia pleuritis and pleurisy with effusion are being widely recognized in tularemia, not as the primary seat of infection but as secondary to a portal of entry on the skin These patients have cough, tenacious blood tinged sputum, dyspnea or pain in the chest, or they may manifest marked respiratory distress but without cough or expectoration

Route of Infection—The route of infection of the lungs in tularemic pneumonias is accepted as via the blood stream in the large number of cases having evident skin lesions and regional lymph node enlargement, but lesser evidence of the skin route of infection such as a cut, crack, vesicle and papule on the hand and transient pain and tenderness in the regional lymph nodes is equally productive of blood stream infection Even the absence of any skin lesion at the point of penetration by the infection has ample support in experimental animals and in laboratory infections of man The clinical observation made in an occasional case history of pneumonia that no skin lesion or enlarged external lymph nodes were found is no justification for drifting to acceptance of the most unlikely route of inhalation

Experimental propulsion of *B tularense* into the trachea by spraying or the inhalation of *B tularense* by aerosol exposure even if sucessful in causing pneumonia would not be acceptable evidence of natural inhalation of the infection

Common observation supports the noncontagiousness to man of the environmental air of patients sick with tularemic pneumonia and of the environmental air of laboratory guinea pigs rabbits and white mice sick and dying of tularemia Laboratory attendants, who only clean cages and feed tularemic animals without handling them, and visitors

death without mutilation in pure undiluted, neutral glycerine and kept continuously at 14° Centigrade at which temperature glycerine does not freeze Four strains so treated by Francis[46] were still of maximum virulence two after 15 years and two after 10 years, and all still await future testing for longevity of virulence

Spleens of infected guinea pigs or rabbits, if dropped into pure undiluted glycerine and placed in the ice box at 5° Centigrade will remain virulent for at least a month thus affording a means of shipping live virus for identification Liver is inimical to the life of *Bacterium tularense* and should not be placed in glycerine in the same container with spleen tissue

Diagnosis

The aids to diagnosis of tularemia are many because there is so little about the disease that is left unknown Thirty proved sources of human infection and thirteen potential sources in the United States have been listed in a previous section of this chapter The tentative diagnosis of tularemia could scarcely escape thought in a febrile patient who had skinned dressed or been bitten by any of the listed animals especially wild rabbits and who now presented an ulcer of the hands or a conjunctivitis accompanied by regional lymph node enlargement A history of fly bite on the uncovered skin or tick bite under the clothing or of crushing of ticks or flies between the fingers and now accompanied by regional lymph node enlargement suggests tularemia The clinical pictures of flu bronchitis pneumonia psittacosis typhoid brucellosis tuberculosis with pleural effusion septic infection or sporotrichosis should arouse suspicion of tularemia The oculoglandular type of tularemia has suggested Parinaud s conjunctivitis Granulomatous lymph nodes in tularemia have suggested tuberculosis to the pathologist Serologists by their failure to test suspected serums against both *B tularense* and *Brucella abortus*, have been misled by gross agglutinins The laboratory methods of diagnosis will be described under (1) agglutination (2) cross agglutination (3) skin test (4) diagnostic therapeutic test with streptomycin (5) isolation of culture from man (6) animal inoculations Microscopic examination of cover glass preparations taken direct from the patient is useless for diagnosis

(1) *Agglutination* – The agglutination[4, 112] test in tularemia is one of the most reliable in the whole field of serology Agglutinins are absent from the blood during the first week of illness but blood taken in the be

Cutaneous Inoculation—Not only can the infection be indefinitely propagated in the laboratory from rodent to rodent by rubbing infected tissue on the shaven, abraded skin, but infection also readily takes place through the unshaven, unabraded and unrubbed skin of a guinea pig or rabbit when infectious material is applied very gently between the hair to the animal's normal skin

Transmission by Feeding—Guinea pigs, rabbits, white mice, opossums and to a less extent cats, dogs, rats and red foxes, become infected after eating food which has become artificially contaminated with infected animal tissue or after eating infected animals White mice readily eat bedbugs and constantly become infected after eating infected bedbugs Mice eat each other and become infected after eating an infected mouse

Nasal Secretions, Urine and Feces—Rabbit urine and nasal secretions cause tularemia by subcutaneous injection but not by feeding, mouse urine acts in the same way, tick feces and bedbug feces are very infectious by inoculation into guinea pigs

Drying—Two lots of infected bedbug feces dried at room temperature on filter paper caused death of guinea pigs from tularemia when injected subcutaneously after 20 and 25 days, respectively, of drying

Formalin—Cultures suspended in saline solution containing 0 1 per cent to 0 3 per cent of formalin (37 per cent strength) are rendered non-virulent after 24 hours

Trikresol—Spleen tissue rubbed up in 1 per cent trikresol, was free from infection after 2 minutes

Heat—56 to 58 C kills the organism in cultures and in spleen tissue in ten minutes Thorough cooking renders infected tissue harmless

Refrigeration—Artificially infected rabbit carcasses, unmutilated except for removal of stomach and intestines at the moment of death were frozen immediately at 14 C by Francis[86] and thereafter kept continuously at that temperature without thawing At six months intervals tissues of the rabbits were tested for survival of infection by injection into guinea pigs Virulent organisms survived 42 months in spinal cord 36 months in brain 18 months in spleen, 12 months in muscle and liver and 6 months in bone marrow Heart blood of guinea pigs drawn in half cubic centimeter amounts, into glass pipettes which were then sealed at each end and kept continuously at -14 C, was found virulent when tested at six months intervals up to 24 months but not longer

Preservative Effect of Glycerine—Virulence of *Bacterium tularense* is long maintained in guinea pig spleen immersed at the moment of

(5) *Isolation of B tularense from Man*—The cystine requirement for growth of *B tularense* makes blood glucose cystine agar or coagulated hen s egg yolk necessary for obtaining a culture at the bedside direct[8, 111] from the patient s blood pleural fluid ascitic fluid or conjunctiva For ease and certainty of isolation human tissue and fluids are inoculated first into guinea pigs rabbits or white mice culture mediums are inoculated from these animals before their impending death or soon thereafter

(6) *Animal Inoculation*—Scrapings or washings from the site of the fly bite or tick bite from other sites of infection from the patient s suppurating lymph nodes or from tissue from a wild rabbit s spotted spleen or liver should be injected subcutaneously over the abdomen of mice guinea pigs or rabbits such material should first be rubbed in a mortar suspended in salt solution and strained through coarse gauze Within a week the animals should die presenting a gray granular caseation of the lymph nodes of the groin and great numbers of small white foci of necrosis studded over the enlarged spleen especially and over the liver The organs should be viewed in direct sunlight or in strong electric light In the absence of apparent lesions the death of the animal is sufficient incentive for carrying over to a fresh animal

Material from the dead animal s lymph nodes spleen and liver when rubbed on the shaven abraded skin of another guinea pig or rabbit should likewise cause its death within a week with the same typical lesions of the lymph nodes spleen and liver and thus the infection may be propagated for an indefinite number of passages through guinea pigs or rabbits

Cultures of *Bacterium tularense* may be obtained by inoculation from the blood spleen or liver of these animals to coagulated egg yolk or blood glucose cystine agar on which media the organism grows as a small non motile gram negative rod while on plain agar no growth will take place The bacteriological diagnosis of tularemia should rarely be expected from cultural inoculations or from smears made direct from the patient

More reliance should be placed on the gross pathological evidence of the disease in guinea pigs or rabbits than on direct microscopic findings in the patient or animal

Prevention

Keep the bare hands out of a wild rabbit Rubber gloves afford reasonable protection to those who must dress wild rabbits and other ani

ginning of the second week usually will show agglutination of *B tularense* in dilution of 1 20, this titer increases on each succeeding day to 1 40 1 80 1 160 1 320, until a titer of 1 640 is reached by about the fourteenth day of illness In rare cases agglutinins do not appear until the third week The agglutinin titer usually reaches its maximum of 1 1 280 1 2,560 or 1 5,120 by the end of the third or fourth week, when a decline in titer begins Persistence of some degree of agglutination however, remains for years in the blood of patients, who have recovered, and is a notable and fortunate occurrence in proof of infection, which took place as long as 20 to 30 years previously

(2) *Cross agglutination*—The serum from a tularemia case often will show agglutination not only of *B tularense* but also to a less degree for *Brucella melitensis, Brucella abortus* and *Brucella suis* Vice versa the serum from a case of brucellosis may agglutinate not only the brucella cultures but, to a less degree, may agglutinate *B tularense*

On first thought this cross-agglutination may seem to be a serious objection to the reliability of the agglutination test in the diagnosis of both tularemia and brucellosis, but such is not the case provided the tests are made by a competent serologist It should be routine in any serological laboratory to test serums suspected of being from either tularemia patients or from brucellosis patients against a killed tularense culture and against a killed brucella culture If in reality the patient has tularemia, his serum will agglutinate *B tularense* more quickly and to a higher titer than it agglutinates the brucella culture but if in reality the patient has brucellosis the serum will agglutinate a brucella culture more quickly and to a higher titer than it agglutinates *B tularense* The tests should remain in the water bath for 2 hours then be transferred to the cold room over night and read the next morning In case the tularense and the brucella titers are the same or nearly so the serum should be subjected to the agglutinin absorption test which will give the final diagnosis as to whether tularemia or brucellosis is the cause of the patient's illness

(3) *Skin Test*—Foshay has introduced a killed bacterial suspension of *B tularense* for intradermal testing as an aid to early diagnosis Hypersensitivity of the skin is a notable feature of tularemia and for that reason great caution should be exercised in selecting an antigen for skin testing because of the danger of causing a local violent reaction at the site of the test

(4) *Diagnostic Therapeutic Test with Streptomycin*[99]—See under treatment

(5) *Isolation of B tularense from Man*—The cystine requirement for growth of *B tularense* makes blood glucose cystine agar or coagulated hen s egg yolk necessary for obtaining a culture at the bedside direct[111] from the patient s blood pleural fluid ascitic fluid or conjunctiva For ease and certainty of isolation human tissue and fluids are inoculated first into guinea pigs rabbits or white mice culture mediums are inoculated from these animals before their impending death or soon thereafter

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Prevention

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mals, but sharp fragments of rabbit bone can easily pierce a rubber glove and puncture the hand Employ immune persons when contact with infected material is necessary Thorough cooking of all wild game especially rabbits is essential Infected meat is rendered harmless for food by thorough cooking, but if any red juice is allowed to remain about the bones the germs will remain alive and virulent in it The liberal use of soap and water and disinfection of the hands are recommended to remove rabbit blood from the hands or even when the hands have come in contact with the rabbit's fur The ordinary disinfectants are effective Disinfection of bites, cuts, punctures and scratches should be practiced, but this measure often has failed to prevent infection Disinfection of ulcers, abscesses, sputum, conjunctival secretion, urine and feces of patients would seem indicated, but no case has been traced to these sources Isolation, quarantine and house disinfection are not indicated

Treatment

Rest in bed is important Those who have had the most experience with the enlarged lymph nodes, do not advise excision or even incision until a very evident soft thin place appears in the skin overlying the nodes No preventive vaccine or curative antiserum has yet been perfected *Streptomycin is by far the drug of choice for the* treatment of tularemia and is described in the next section

Treatment with Streptomycin

The bactericidal action of streptomycin against *B tularense* in man and animals makes this new antibiotic the ideal weapon of attack in tularemia a disease which is characterized by a rapidly disseminating bacteremia Streptomycin is an antibiotic discovered by Waksman[13] and is produced by the growth of *Streptomyces griseus* on culture medium It is prepared as a hydrochloride or sulphate salt and is marketed as a sterile powder in airtight vials containing 1 gram each which should be stored unopened at a temperature not higher than 15° C At time of use the entire 1 gram contents should be dissolved by the addition of 5 c c of pyrogen-free distilled water or physiological saline solution to the vial which then is kept in the refrigerator and used within 24 hours For daily injection of 1 gram the vial contents are injected intramuscularly

in divided doses of 125 mgm every 3 hours day and night, at each injection give one eighth of the contents of the vial injecting slowly into the gluteal thigh or deltoid muscles

Potency was expressed originally in units but now by weight one microgram corresponding to one unit or 1 gram to 1 000 000 units

Toxicity of Streptomycin —Toxicity of the drug has been well summarized by Keefer and associates[100], not only for the information of physicians but as a warning to be given to all patients before starting the drug Pain at the site of intramuscular injection may be alleviated by the addition of 1 c c of 1 per cent procaine hydrochloride to each 4 c c of solution before injection without causing inactivation of the streptomycin One should watch the patient for skin eruptions and fever for neurological disturbances vertigo tinnitus deafness for histamine like effects consisting of headache flushing of skin nausea fall in blood pressure Miscellaneous effects may be diarrhea albuminuria and casts in the urine purpura hemorrhagica arthralgia eosinophilia

This array of toxic symptoms of the drug has not been experienced in tularemia which requires comparatively small doses but only in prolonged treatment with large doses in chronic diseases like tuberculosis and leprosy The extreme of toxicity is death and 2 such fatalities with histamine like reactions are known to have occurred Toxic symptoms actually reported in cases of tularemia treated with streptomycin have been limited to macular rash in one case

Clinical Response to Streptomycin — 'Amazing is the word most descriptive of the changed condition of the acutely ill tularemic patient at the end of the first 24 hours of streptomycin treatment headache is gone the mental stupor has cleared, the temperature has fallen chilly sensations have disappeared aching of the muscles and joints is gone nausea has ceased prostration has been relieved the patient feels comfortable The clinical changes are in harmony with the proof of the bactericidal action[9] [90] of the drug on *B tularense* in vivo and vitro and give streptomycin the distinction of being a specific in the treatment of tularemia Less striking are the immediate changes in pathological processes in the primary ulcer lymph nodes pneumonic consolidations and pleural effusions These processes require almost the usual time as in the untreated patient

Long persistence of agglutinins which is a notable feature of tularemia appears to be unaltered by streptomycin treatment

Recommended Dosage in Tularemia —One gram per day for 5 days given intramuscularly in divided doses every 3 hours day and night is

a good working guide to dosage Five grams or less was the total amount received by each of 31 recorded patients, 11 of which had bronchopneumonia (Hunt)[39] and 3 others had lobar pneumonia Eighteen other patients received a total of over 5 grams each, the 6 largest amounts per patient being 17, 18, 22, 29, 32 and 32 grams This latter group of 18 cases included 15 patients with either lobar pneumonia or bronchopneumonia which probably accounts for their larger doses in the hope of combating the grave prognosis of the pulmonary type of the disease For tabulation of dosage in reported cases see Francis[81]

There is no occasion for giving streptomycin in every case of tularemia the general mortality of which is only 7 4 per cent of the total number of reported cases It is in the highly fatal pleuropulmonary type that life-saving is expected to contribute most to reduction of the general mortality rate of the disease Severe cases of whatever type including the meningeal and ingestion types, are not best treated unless they get streptomycin

Case Reports—Detailed reports of 43 cases of tularemia treated with streptomycin have appeared in the literature, of these 7 cases were reported by Foshay and Pasternack,[80] 7 by Howe and associates[18] 12 by Hunt[39] and 17 by the authors of 12 other papers listed in the bibliography Notes on unpublished cases are on hand The reports attest the greatest value of the drug in the acute severe stages of the disease Four cases treated respectively 103, 120, 156 or 334 days after onset and one treated in "convalescence" showed no response to the drug

Diagnostic Therapeutic Dose of Streptomycin—Case reports show that patients in diagnostic doubt and treated within a few days by a sequence of penicillin sulfadiazine and streptomycin showed improvement only after streptomycin, thus establishing the tularemia diagnosis and pointing the way to prompt streptomycin recovery Persons first seen in stupor, unconsciousness or coma, have revealed the true diagnosis of tularemia following a therapeutic diagnostic test dose of streptomycin which clarified their mental state and permitted rational recital of tick bite or rabbit contact, thus indicating immediate further continuance of streptomycin for their tularemia

Streptomycin in diagnostic dosage will differentiate tularemic pneumonia from other types of pneumonia not due to *B tularense* The importance of early diagnosis and streptomycin treatment of tularemic pneumonia has been recognized by all observers as a life saver in this highly fatal type of tularemia Hunt[39] suggests 1 to 2 grams daily for

4 days as an adequate diagnostic therapeutic test in cases of severe pneumonia of undetermined origin in endemic tularemia areas

PROGNOSIS

Mortality in Tularemia Before Advent of Streptomycin —During the 23 years (1924 1946) before the discovery of streptomycin the number of cases of tularemia reported by State Health Officers to the U S Public Health Service was 20 562 and the number of deaths recorded by the United States Office of Vital Statistics was 1 53 giving a mortality of 7.4 per cent which included all clinical types of tularemia But analysis of the seven clinical types of the disease showed great variation in mortality Twelve of 20 cases of the ingestion type died and of 6 cases of the meningeal type all died The pulmonary type variously referred to as pleuropulmonary pleuropneumonic and tularemic pneumonia showed a mortality of 46 7 per cent of 109 pulmonary cases analyzed by Francis[87] Stuart and Pullen[118] in analyzing 68 cases of tularemic pneumonia collected from the literature including 15 cases of their own found a mortality rate of 39 9 per cent Blackford and Casey[83] reported a mortality of 35 per cent of 20 cases of tularemic pneumonia

Post streptomycin Mortality —The pulmonary type of tularemia by reason of its large number of cases and their high mortality rate presents the severest therapeutic test in tularemia In Keefer's[100] enumeration of 67 cases of tularemia treated with streptomycin there was 1 death on the first day of treatment the patient being 1 of 11 manifesting pleural or pulmonary involvement In Hunt s[99] report of 12 cases of tularemic bronchopneumonia treated with streptomycin one patient died suddenly during convalescence on the seventh day of treatment and on the 38th day of illness apparently from a massive pulmonary embolism there was no autopsy In another group of 8 unreported cases 5 of which manifested pneumonic manifestations all responded well to streptomycin

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